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# Section A

## Biological Sciences and Clinical Medicine

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# LONGEVITY AND THE ONSET OF LESIONS IN MALE RATS*

HENRY S. SIMMS, PH.D., AND BENJAMIN N. BERG, M.D.
*(From the Department of Pathology, College of Physicians and Surgeons, Columbia University, New York)*

It is self-evident that longevity is related to mortality and that mortality is the direct result of disease. The relation of age to mortality rates has been discussed in several papers from this laboratory (7,8,9,10). However, little has been known about the relation of age to the accumulation of the lesions of disease.

## METHODS

In order to explore this field, a special rat colony was established in 1945† with animals raised under as uniform and as ideal conditions as circumstances permitted:

1. The temperature was maintained at 76 F.
2. The humidity was maintained at 60 per cent.
3. The diet was uniform (Rockland "D-free" rat diet), with a constant food supply in each cage.
4. The lighting was uniform and indirect, being reflected from walls having a uniform color.
5. The lights were governed by a time switch, giving 12 hours of light and 12 hours of darkness each day throughout the year (all outside light being excluded).
6. All rats which had been used as breeders were discarded and were not placed with the experimental rats.
7. Special cages and shelves were designed. The cages hold 3 or 4 animals each.
8. Shavings were used in preference to wire mesh floors in the cages.
9. Wire mesh windows on the sides of the cages permitted the rats to become acquainted with their neighbors.
10. The caretakers were all one sex (female).
11. The male and female rats were kept in separate quarters.
12. Noise and rough handling were eliminated in so far as possible.
13. The system of filling water bottles prevented the transfer of bottles from one cage to another. Fresh water was always present.
14. Each rat was tattooed to identify its litter and ear-punched for individual identification.
15. Careful records were kept on every rat from breeding to autopsy. These records included weight data and information on apparent health.

The rats have been bred from an original shipment (in 1945) of Sprague-Dawley rats. An eye anomaly, which was present among the early animals, was eradicated by selective breeding. Otherwise the breeding has not been intentionally selective. Respiratory infection has been reduced to a low incidence. This was accomplished by the elimination of all obviously infected animals, those suspected of infection, and those whose weight curves showed plateaus.

### *Autopsies*

As each rat was thought to have reached a moribund state it was killed with nembutal injected intraperitoneally and a complete au-

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† This animal colony was established in a building owned by the Presbyterian Hospital and was first made possible by grants from the Josiah Macy, Jr., Foundation and the Albert and Mary Lasker Foundation. Subsequent support has come largely from Grant H-945 from the National Heart Institute of the U. S. Public Health Service. Grants have also been received from the Muscular Dystrophy Association of America.

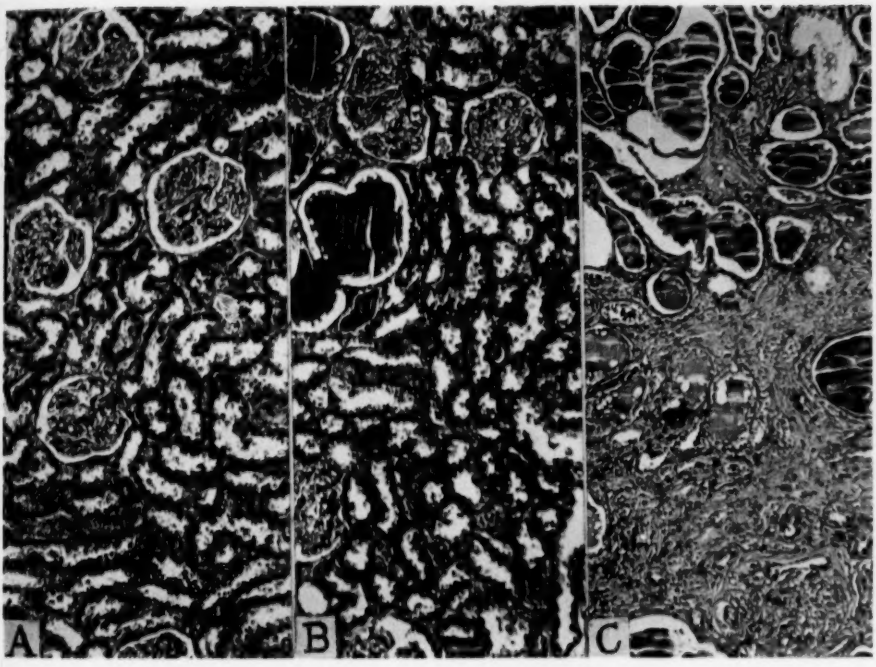


Fig. 1. An example of the progressive development of lesions. All 125X.
A. Section of normal kidney.
B. Early (mild) renal lesion. Dilated proximal convoluted tubules containing casts.
C. Severe renal lesion. Extensive destruction and fibrosis of the parenchyma. The glomeruli have disappeared except for a single degenerated tuft whose outline is still visible. The remaining tubules are in various stages of dilation and degeneration.

topsy was performed immediately. Those animals that died in their cages were autopsied as soon as possible. A few animals in the lower age groups were killed in a non-moribund state in order to supplement the data on the younger rats. The autopsies during the past 6 years were performed, and the sections examined, by one pathologist. He was aided by a succession of laboratory assistants. The data on each lesion were carefully recorded. The accumulated data from over 2,000 autopsies have been tabulated on special record sheets to facilitate statistical evaluation. Some of our observations on the diseases in these rats have been published in previous papers (1, 2, 3, 4, 11).

*Severity of Lesions.*—According to the degree and extent of lesions, they were graded as early, moderate, or severe. This classification was based on gross and histologic findings interpreted by a single observer. Grading was approximate but sufficiently adequate for the purposes of this study.

*Five Selected Diseases*

This paper deals with the data on the lesions found in 1,410 male rats. For this preliminary report 5 diseases of major importance in the rat have been selected for statistical study. These diseases and their characteristics are as follows:

*Chronic Nephrosis and Glomerulonephritis.*—Early histologic changes consist of dilatation with flattening of the lining epithelium of some of the proximal convoluted tubules. In the next stage (moderate severity) there is further dilatation of more tubules including the collecting system, with atrophy of corresponding glomeruli. Lesions rated as severe correspond to the findings in chronic glomerulonephritis. The parenchyma shows extensive destruction and is replaced by numerous cysts of variable size resulting from dilated tubules. Most of the glomeruli disappear, are atrophic, or are hyalinized. There is a relative increase in connective tissue often infiltrated by lymphocytes. The media

TABLE 1. NUMBER OF RATS HAVING LESIONS OF FIVE MAJOR DISEASES.
O = no lesions. E = "early" (slight) lesions. M = moderate lesions. S = severe lesions.

| Age Range (Days) | Total No.* | Chronic Nephrosis and Glomerulonephritis | | | | Myocardial Degeneration | | | | Periarteritis | | | | Muscular Degeneration* | | | | Adenoma of the Pituitary | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | O | E | M | S | O | E | M | S | O | E | M | S | O | E | M | S | O | E | M | S |
| 0— 99 | 15 | 15 | 0 | 0 | 0 | 15 | 0 | 0 | 0 | 15 | 0 | 0 | 0 | — | 0 | 0 | 0 | 15 | 0 | 0 | 0 |
| 100— 199 | 33 | 27 | 5 | 1 | 0 | 33 | 0 | 0 | 0 | 33 | 0 | 0 | 0 | — | 0 | 0 | 0 | 33 | 0 | 0 | 0 |
| 200— 299 | 46 | 46 | 0 | 0 | 0 | 45 | 0 | 1 | 0 | 45 | 0 | 0 | 1 | — | 0 | 0 | 0 | 46 | 0 | 0 | 0 |
| 300— 399 | 33 | 23 | 5 | 3 | 2 | 29 | 1 | 3 | 0 | 31 | 0 | 0 | 2 | — | 0 | 0 | 0 | 33 | 0 | 0 | 0 |
| 400— 499 | 72 | 61 | 8 | 1 | 2 | 70 | 1 | 1 | 0 | 69 | 0 | 1 | 2 | — | 0 | 0 | 0 | 72 | 0 | 0 | 0 |
| 500— 599 | 92 | 40 | 22 | 22 | 8 | 65 | 6 | 14 | 7 | 83 | 0 | 2 | 7 | 57 | 0 | 0 | 1 | 83 | 0 | 1 | 8 |
| 600— 649 | 64 | 27 | 8 | 16 | 13 | 42 | 0 | 17 | 5 | 52 | 1 | 3 | 8 | 31 | 1 | 1 | 2 | 54 | 0 | 1 | 9 |
| 650— 699 | 112 | 19 | 25 | 26 | 42 | 61 | 3 | 35 | 13 | 79 | 4 | 9 | 20 | 66 | 0 | 0 | 1 | 92 | 0 | 0 | 20 |
| 600— 699 | 176 | 46 | 33 | 42 | 55 | 103 | 3 | 52 | 18 | 131 | 5 | 12 | 28 | 97 | 1 | 1 | 3 | 146 | 0 | 1 | 29 |
| 700— 749 | 121 | 8 | 30 | 36 | 47 | 55 | 3 | 31 | 32 | 71 | 1 | 13 | 33 | 41 | 0 | 8 | 6 | 98 | 0 | 4 | 19 |
| 750— 799 | 131 | 13 | 13 | 48 | 57 | 60 | 5 | 36 | 30 | 61 | 5 | 13 | 52 | 16 | 5 | 19 | 10 | 105 | 0 | 3 | 23 |
| 700— 799 | 252 | 21 | 43 | 84 | 104 | 115 | 8 | 67 | 62 | 135 | 6 | 26 | 85 | 57 | 5 | 27 | 16 | 203 | 0 | 7 | 42 |
| 800— 849 | 187 | 36 | 13 | 67 | 71 | 68 | 7 | 51 | 61 | 79 | 2 | 32 | 74 | 24 | 5 | 28 | 26 | 130 | 1 | 8 | 48 |
| 850— 899 | 185 | 25 | 10 | 70 | 80 | 60 | 3 | 46 | 76 | 78 | 0 | 26 | 81 | 14 | 5 | 22 | 44 | 145 | 1 | 9 | 30 |
| 800— 899 | 372 | 61 | 23 | 137 | 151 | 128 | 10 | 97 | 137 | 157 | 2 | 58 | 155 | 38 | 10 | 50 | 70 | 275 | 2 | 17 | 78 |
| 900— 949 | 159 | 7 | 7 | 58 | 87 | 36 | 1 | 47 | 75 | 56 | 0 | 32 | 71 | 7 | 0 | 14 | 45 | 119 | 0 | 13 | 27 |
| 950— 999 | 90 | 7 | 3 | 42 | 38 | 26 | 3 | 17 | 44 | 39 | 0 | 18 | 33 | 3 | 0 | 8 | 29 | 77 | 0 | 4 | 9 |
| 900— 999 | 249 | 14 | 10 | 100 | 125 | 62 | 4 | 64 | 119 | 95 | 0 | 50 | 104 | 10 | 0 | 22 | 74 | 196 | 0 | 17 | 36 |
| 1000—1099 | 67 | 2 | 2 | 33 | 30 | 13 | 1 | 12 | 41 | 29 | 0 | 6 | 32 | 0 | 0 | 7 | 27 | 54 | 1 | 8 | 4 |
| 1100—1250 | 3 | 0 | 0 | 2 | 1 | 1 | 0 | 1 | 1 | 2 | 0 | 0 | 1 | 0 | 0 | 0 | 1 | 3 | 0 | 0 | 0 |
| 1000—1250 | 70 | 2 | 2 | 35 | 31 | 14 | 1 | 13 | 42 | 31 | 0 | 6 | 33 | 0 | 0 | 7 | 28 | 57 | 1 | 8 | 4 |

* The number of rats examined for muscular degeneration was less than the "Total No." in column 2.

and intima of medium and small sized arteries are frequently thickened.

Marked weight loss, weakness, and lethargy develop as the disease progresses. Hypertension and cardiac hypertrophy are common complications and when renal failure sets in the non-protein nitrogen of the blood increases. Ascites and hydrothorax are frequent, but edema is rare.

*Myocardial Degeneration.*—Atrophy, fibrosis, and necrosis develop in the myocardium and occur in order of decreasing frequency in the papillary muscle and adjacent area of the left ventricle, at the base of the heart, around the branches of the coronary arteries, at the apex, and in the interventricular septum. Slight myocardial damage restricted to a single area is graded as early. Greater degeneration often involving more than one site is classified as moderate. Extensive lesions occurring in several places are considered to be severe.

Due to the nature and distribution of myocardial lesions the disease may be regarded as a contributory rather than a chief cause of death.

*Periarteritis.*—The disease affects chiefly the mesenteric and spermatic arteries but also may involve other vessels such as the hepatic, adrenal, thyroid, coronary, renal, or pulmonary. Changes in the arteries are essentially a focal degeneration and inflammation of the media and adventitia leading to the formation of aneurysms that become occluded by thrombi or may rupture. The vessels have a beaded appearance. Lesions occur first in the arteries of the pancreas and testes. In the pancreas, zones of atrophy, degeneration, and fibrosis sur-

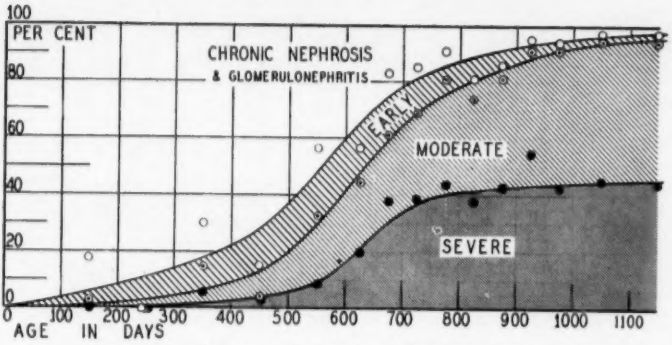


Fig. 2. Incidence of lesions of chronic nephrosis and glomerulonephritis found on autopsy in 1410 male rats, expressed as percentage of animals having lesions at different ages.

In each of the charts (figs. 2-6) the bottom curve indicates the severe lesions, the middle curve the severe plus moderate lesions, and the top curve the total of all degrees of severity.

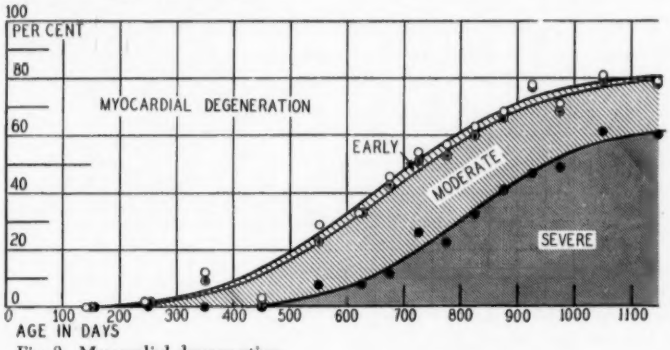


Fig. 3. Myocardial degeneration.

round diseased vessels. Ascites is a frequent complication.

When alterations are minimal and are limited to a single vessel in the pancreas they are termed early. More marked changes extending to the upper mesenteric arteries are rated moderate. Lesions graded severe involve all of the mesenteric vessels and are characterized by aneurysms.

*Skeletal Muscle Degeneration.*—Early signs of muscle degeneration are loss of cross striations and narrowing of scattered fibers. Moderately advanced alterations are characterized by fragmentation and disintegration, and larger numbers of fibers are involved. Severe changes consist of extreme necrosis and disappearance of fibers leaving empty sarcolemma sheaths. Lesions occur in patches interspersed among normal muscle bundles.

The disease affects chiefly the gastrocnemius and adductor muscles of the hind legs. In some instances other muscles are also involved. Early signs are weakness and unsteadiness of hind legs. Later there is complete, flaccid paralysis which leads rapidly to inanition and death.

*Adenoma of the Pituitary.*—The tumor arises from the anterior lobe of the pituitary and is an adenoma of the chromophobe type. Sometimes the cells are anaplastic and show malignant changes. Hemorrhage, infarction, and necrosis are common. Large tumors destroy neighboring parts of the brain and lead to death by pressure on the vital centers. Symptoms depend upon extent of cerebral damage. Severe weakness, paralysis or convulsions, often sudden in onset, usher in the disease. Polyuria and polydipsia are striking symptoms in some animals. Rating of lesions is based upon size and weight of the tumor.

## RESULTS

The data on the incidence of the 5 diseases are summarized in table 1. As an example of

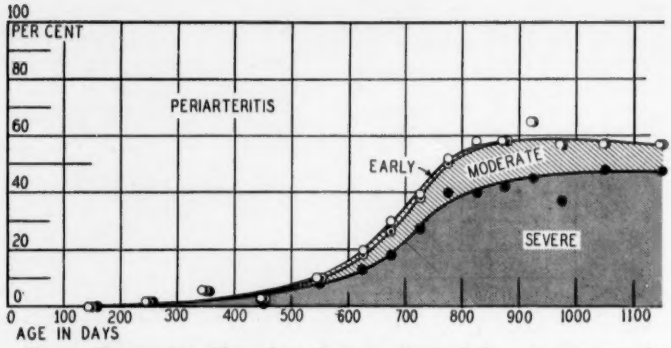


Fig. 4. Periarteritis. Note that about one-third of the rats appear to be non-susceptible, as discussed in the text.

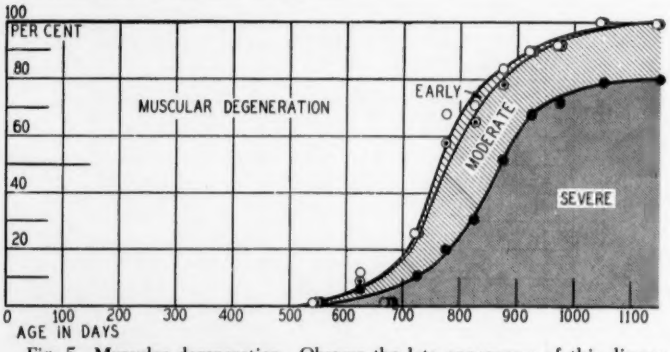


Fig. 5. Muscular degeneration. Observe the late appearance of this disease and the rapid rise of its incidence.

the progress of lesions, the photographs in figure 1 show normal kidney tissue, an early (mild) lesion, and a severe lesion of chronic nephrosis.

In figure 2 the data on chronic nephrosis and glomerulonephritis are represented. The bottom curve shows the percentage of animals in different age groups having severe lesions of this disease. The middle curve indicates the percentage of animals with severe lesions plus those with moderate lesions, and the top curve includes animals having lesions of all degrees of severity (severe, moderate, or early). In this particular disease there is some scattering of points, but the smooth curves have been drawn with considerable care to permit interpolation for subsequent calculations. Each curve is a sigmoid curve starting early in life. The total lesions are seen to approach 100 per cent incidence in older animals.

Figure 3 shows myocardial degeneration. Here there is less scattering of points. The curves are seen to start around 200 days of age —but they approach a level somewhat less than 100 per cent in late life. It will be noted that the number of early lesions is small in all age groups. This indicates a rapid development to lesions of greater severity.

Figure 4 shows the data on periarteritis. These curves approach a level considerably below 100 per cent. This suggests that about ⅓ of the animals may not be susceptible to periarteritis and might not acquire it even if they lived far beyond the range of this study. Although this is a closed colony, it cannot be considered to be completely homogeneous, and there may very well be genetic differences in the susceptibility to this disease. By selective breeding from a colony of Sherman rats in which an early periarteritis was prevalent, Zucker (13) was able to obtain a strain free from this disease.

Figure 5 shows the lesions of muscular degeneration. This is a disease of the voluntary muscles which has some similarity with muscular dystrophy in man. It will be seen that

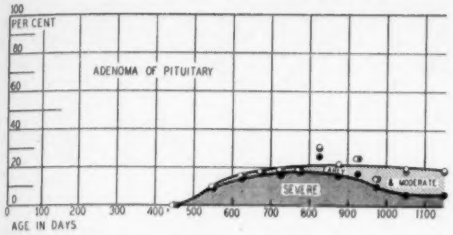


Fig. 6. Adenoma of the pituitary. Note that this neoplasm appears to be limited to a small portion of our rat population.

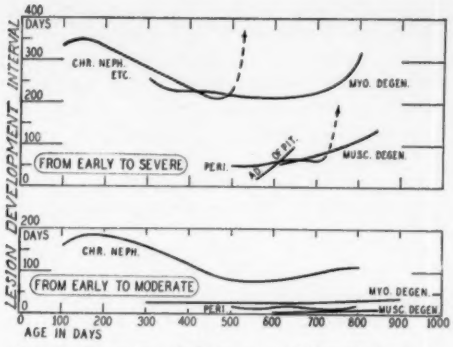


Fig. 7. Duration of diseases at different ages.
Bottom chart: Time for early lesions to develop into lesions of moderate severity.
Top chart: Time of development from early to severe lesions.

no lesions are observable until after 500 days of age—and that the incidence rises rapidly until 100 per cent of the animals are affected by about 1100 days.

For this preliminary paper we have selected one tumor—adenoma of the pituitary. In figure 6 it will be seen that the curves are quite different from 4 charts 2 to 5. These curves approach a maximum of less than 25 per cent of the animals—and then fall off in the higher age groups. The falling off may be accounted for by the fact that many of the susceptible animals had already acquired the disease and had been eliminated by death.

## INTERPRETATION OF DATA

*Duration of Disease.*—One of the purposes of this study has been to determine whether or not the rate of development of lesions, from the early to the late stages, varies with age of the animal. We can now obtain a rough measure of the time required for a lesion to develop. In figures 2 to 6 it will be seen that we can measure off the horizontal distance between the curves. For example, at 650 days in figure 3 the time interval between the top two curves is 25 days, and this indicates the time required for early lesions to develop into moderate lesions. Similarly, the interval, measured horizontally, between the top and bottom curves is about 225 days—representing the time required for an early lesion to develop into a severe lesion.

In figure 7 there are two charts showing these intervals for the 5 diseases under discussion. Although the development-intervals for the 5 diseases are at different levels, it will be noted that the curves are, for the most part, horizontal. In other words, the duration of the diseases as measured by the time interval from early lesions to the moderate, or to the severe, lesions, does not change markedly with age—certainly not enough to account for the increase in mortality with age.

*Probability of Onset of New Lesions.*—Another important problem is the effect of age on the probability of onset of new lesions. In figure 8 we see the sigmoid curves of all 5 diseases under consideration. Each curve is identical with the top curve of one of the first 5 charts, and indicates the percentage incidence ($100\ L/N$) of total lesions (whether early, moderate, or severe) in each age group, where $L$ is the number of rats having lesions and $N$ is the total number of animals in that age group.

On any of these curves the difference in height at two ages 100 days apart represents the increase in lesions within a 100-day period.

$$1) \qquad 100P_N = 100\left(\frac{L_2}{N_2} - \frac{L_1}{N_1}\right)$$

Values of $100\ P_N$ (computed by equation 1 from data obtained graphically from the smooth curves of figure 8) are plotted in figure 9. $P_N$ represents the probability of onset of new lesions within 100 days among the total number $N$ of rats in each age group (including those that had previously acquired lesions). These curves show the distribution of the probability of onset of new lesions. Obviously this is a function of age. It will be seen that for each disease there is an age of maximum probability of onset—and a distribution of values on both sides of this critical age.

*Relation of Lesion Onset to Mortality.* We can now show that the long-known logarithmic

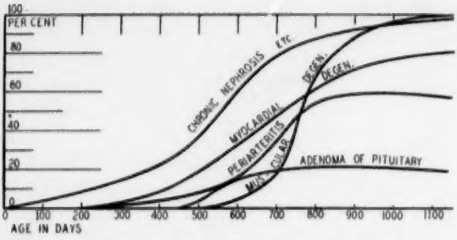


Fig. 8. Percentage incidence $100L/N$ of lesions of these 5 diseases—total of all degrees of severity. Each curve is identical with the top curve in one of the first 5 charts (figs. 2-6).

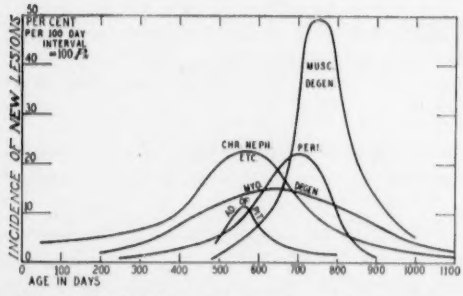


Fig. 9. Probability of onset of new lesions among the total number of rats $N$ alive at each age, expressed as percentage increase 100 $P_N$ per 100-day interval. Computed by equation 1.

increase in mortality with advancing age* is directly connected with this age distribution of new lesions: If a value read from a curve in figure 8 is divided by the percentage of rats at that age having no lesions (of the disease in question) we obtain the ratio of rats having lesions to those without lesions, or $L/(N\text{-}L)$. Differences at 100-day intervals give us the probability values plotted in figure 10:

$$3) \qquad P_L = \frac{L_2}{N_2 - L_2} - \frac{L_1}{N_1 - L_1}$$

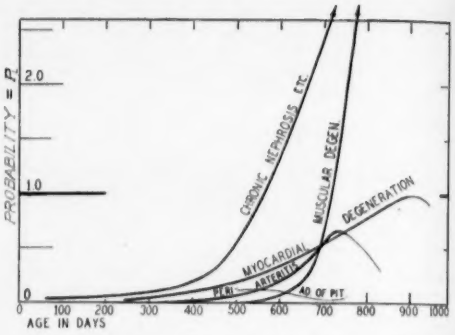


Fig. 10. Probability of onset of new lesions $P_L$ among rats having no lesions $N - L$, expressed as increase (per 100-day interval) in the ratio of rats with lesions to those without lesions. See equation 3.

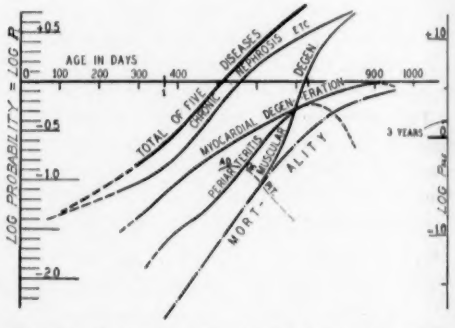


Fig. 11. Logarithm of the probability of onset of new lesions among rats having no lesions (data of fig. 10 plotted as logarithms). Also (top curve) the sum of the probabilities of the 5 diseases, and a curve (bottom) for the mortality of male rats. The scale on the right represents probability of onset in 365 days, for comparison with human data.

where $P_L$ is the probability that a rat of a given age, having no lesion of a given disease, will acquire a new lesion of that disease within 100 days. It is obvious that these are not straight line curves, but that they resemble linear plots of mortality against age (except for adenoma of the pituitary).

The logarithms of the same data are plotted against age in figure 11. It will be noted that the significant portions of these curves are roughly straight lines. This is important since it has been known for a number of years that, for both rat and man, the logarithm of the adult death rate is a linear function of age (see equation 2).

* In 1825 Gompertz (5) showed that human mortality rate increased with age according to an equation which may be written in the following form (9, 10):

$$2) \qquad \log P_M - \log P_{MO} = k_M t$$

where $P_M$ is the probability of death at age $t$, and $P_{MO}$ is the (extrapolated) probability of death at birth. $k_M$ is a positive constant. As this equation indicates, plots of the logarithm of the death rate ($\log P_M$) against age $t$ give curves that are approximately straight lines in the adult age range. As was pointed out by Nathan (6), and later amplified by Simms (7,8,9,10) plots of mortality from specific diseases also give curves that are nearly straight lines—their slope $k_M$ depending on the type of disease. However, the equation is purely empirical and the reason it applies has not been understood.

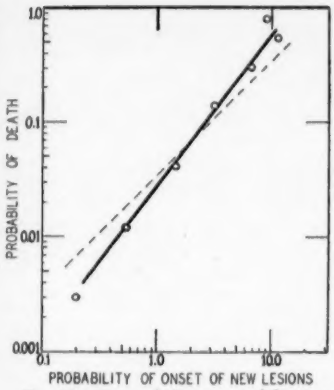


Fig. 12. Data of the top and bottom curves of fig. 11 plotted against each other, showing the relationship between the probabilities of death and of onset of new lesions. The dotted line indicates the slope of perfect correlation.

The top curve in figure 11 represents the sum of the probabilities (of onset of new lesions) of these 5 diseases. The significant portion of this curve is essentially a straight line.

A curve for the mortality of 339 of these rats has been inserted. This curve, which will be seen at the bottom in figure 11, nearly parallels the top curve (for the onset of lesions). In order to demonstrate the close relationship between probability of death and probability of onset of lesions, we have plotted the data of these two curves (the top and bottom ones in figure 11) against each other in figure 12. The equations for the solid line in figure 12 is:

4) $$\log P_M = r \log P_L - q$$

where $r$ and $q$ are constants (for the data in this figure, $r = 1.32$ and $q = 1.55$).

Returning now to the top curve in figure 11: Since it is essentially a straight line, one would expect that it should follow an equation similar to the one (equation 2) for mortality data. Such an equation can be derived* from equations 2 and 4, thus supporting our conclusion that the logarithmic increase in mortality with age can be accounted for by the observed manner of increase in the onset of lesions.

Furthermore it can be shown† that equation 5 is consistent with the assumption that the transition time $\triangle t$ from early lesions to death is either constant with age, or is a linear function of age. This reasoning is independent of any judgment as to severity of lesions.

## DISCUSSION

The longevity of a species is determined by the mortality from the major diseases of that species—and especially by the effect of age on this mortality (12). It has been known for years (5,6,7,8,9,10) that the relation of age to mortality can be expressed empirically by equation 2 and can be represented by charts of the logarithm of death rate plotted against age. Such charts are characterized by curves (such as the bottom curve in fig. 11) which are nearly straight lines throughout adult life.

In our present study, this effect of age has been found *not* to be attributable to the duration of disease. This is demonstrated by the relatively uniform time interval from early lesions to moderate or late lesions. (See fig. 7.)

On the other hand, our data on 5 major diseases in male rats indicate that the effect of age is manifested by a latent period preceding an age of maximum onset of lesions. (See figs. 8 and 9.) The length of this latent period is typical of each disease.

At the same time it should be noted that for this species the latent periods of the selected chronic diseases are all within the range from 1.5 to 2.1 years, whereas we would expect that for chronic diseases in man, for example, the latent periods may be 30 times as long. This indicates that there is a species factor which far outweighs the influence of individual diseases.

Hence, the effect of age on longevity depends upon the relation of age to the susceptibility to chronic diseases (as manifested by the latent periods preceding maximum onset of lesions). At the present time we do not know whether

* From equations 2 and 4 we can write:

$$r \cdot \log P_L = \log P_{MO} + q + k_M t$$

Since $\frac{1}{r}(\log P_{MO} + q)$ is constant, it can be substituted by $\log P_{LO}$; and since $k_M/r$ is also constant, it can be replaced by $k_L$. Therefore:

5) $$\log P_L = \log P_{LO} + k_L t$$

This is the equation for the onset of lesions which applies to the onset curves in figure 11, in so far as they are straight lines.

† At any level of probability such that $\log P_M = \log P_L$ the respective values of $t$ can be designated $t_M$ and $t_L$. By equating 2) and 5), solving for $t_M$, then subtracting $t_L$ from both sides, we get:

6) $$\Delta t = t_M - t_L = (\tfrac{1}{r} - 1)t_L + \text{a constant}$$

and in the case that $r = 1$ we get:

$$\Delta t = t_M - t_L = \text{a constant}$$

or not these latent periods involve degenerative changes in the tissues, or other alterations which might be designated as part of an aging process.

SUMMARY

In a long-term study on longevity, autopsy findings on over 1,400 male rats of all ages, raised under uniform conditions, have been carefully tabulated. The data on 5 major diseases are discussed in this paper.

It is shown that there is little relation between age and the duration of these diseases, as measured by the time interval between early and late lesions.

On the other hand, the probability of onset of new lesions was found to be related to the age of the animal by the same equation that applies to rat (and human) mortality data. Hence, the age of death depends upon the age of onset of new lesions.

For each disease there is: a) an age of maximum probability of onset of lesions, b) a characteristic range of distribution about this maximum value, and c) a limit to the percentage of animals that will acquire each type of lesion.

Thus, longevity of the species is determined largely by those forces that hasten or retard the age changes leading to the onset of lesions of the major diseases of the species.

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# LONGEVITY OF MALE AND FEMALE HOUSE FLIES*

MORRIS ROCKSTEIN, PH.D.

*(From the Department of Physiology, New York University College of Medicine, New York)*

During the course of a rather extended study on the nature of biochemical manifestations of aging, especially as regards motor function in the common house fly, *Musca domestica* L. (9), it was noted that the number of male flies which were available for evaluation of enzyme activity declined rapidly after the second week. This naturally suggested that the male of this species had a shorter lifespan than the female. In several earlier papers (6, 7, 8) and in a recently published handbook (10) average and maximum longevities for a number of species of insects and for a large number of vertebrate species were noted by the present author; Hamilton (3) has also cited reports by a number of observers of the comparative lifespan of males and females of a variety of invertebrate species. Unfortunately, few of these longevity data (for species as a whole or by sex within a species) are based on animals maintained under standardized, controlled conditions of temperature, relative humidity or diet. The study reported upon in this paper was undertaken with the primary objective of determining the longevity of members of this species under conditions established as standard by insect physiologists and entomologists, as well as to test the inference from previous (limited) observations that the female of this species has a greater longevity than the male.

## MATERIALS AND METHODS

Flies from a long-inbred strain of NAIDM house flies were all bred, reared, and maintained in an air-conditioned room at 80 F. and 45 per cent relative humidity. Adult females 4 to 5 days old were allowed to oviposit freely on a suitable medium developed at the Army Chemical Center Entomology Branch. This consisted of 10 per cent Fleischmann's dried brewer's yeast, 10 per cent Klim (Borden's powdered whole, bovine milk) and 1.5 per cent Difco Bacto-Agar, all dissolved in boiling water to 100 per cent; this was then poured hot in known amounts into pint jars and allowed to solidify at a fixed slant, by cooling. About 300 eggs were added to the cooled medium and covered with sterile wood shavings to the top of the jar, which was then covered with a screened Mason-jar cover. Under the temperature and humidity conditions mentioned above, flies emerging on Thursday of one week begin to lay eggs between the Monday afternoon and Tuesday morning of the following week. Such eggs, seeded into rearing jars containing medium, yield adults on the Thursday exactly two weeks after the emergence of their own parents. This two-week cycle permits easy management of medium preparation and egg collection, as well as availability from a long-inbred strain of large numbers of adults for a very narrow age range (less than one hour of age, for example).

In the first preliminary follow-up of earlier observations, about 125-175 flies of both sexes less than 24 hours of age were transferred into each of 5 cages containing unlimited supplies of sugar (sucrose) and water. At each of the intervals indicated in table 1, experiment 1, one cage was removed at random, the dead flies aspirated off and discarded (without being counted), and the living flies inactivated by freezing and counted by sex; some were employed in enzyme studies and the remaining flies were discarded. Because only the *surviving* flies had been collected and counted in the above study, doubt remained as to the original sex ratios in these cages, and, therefore, as to the inferred longer lifespan of the females. Thus, a second study (experiment 2) involving 6 cages, each containing about 100-125 flies of both sexes, was made under conditions otherwise similar to before (i.e., with only sugar and water in the cage). In this experiment, however, *all* the original flies were accounted for by periodic collection, pooling, and counting of the

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The author is greatly appreciative of the cooperation of Dr. Albert S. Perry, of the U.S.P.H.S. Technical Development Laboratories at Savannah, Georgia, in making available flies from which culture could be initiated, as well as of the invaluable technical assistance of Mr. Jack Roemer in this study.

TABLE 1. COMPARATIVE LONGEVITY OF MALE AND FEMALE FLIES.

Experiment 1. Survival Study (5 cages of 125-175 flies each; sugar and water only).

| | Cage 1 | Cage 2 | Cage 3 | Cage 4 | Cage 5 |
|---|---|---|---|---|---|
| Age | 24 hrs. (I) | 24 hrs. (II) | 13 days | 19 days | 21 days |
| Number of Males Surviving..... | 55 | 79 | 30 | 30 | 0 |
| Number of Females Surviving..... | 67 | 68 | 57 | 103 | 136 |

TABLE 2. COMPARATIVE LONGEVITY OF MALE AND FEMALE HOUSE FLIES.

Experiment 2. Mortality Study (6 cages of 100-125 flies each; sugar and water only).

| Age | 12 days | 22 days | 26 days | 28 days | 32 days | 34 days | 43 days |
|---|---|---|---|---|---|---|---|
| Males % Dead. | 13 | 67 | 78 | 88 | 97 | 99 | 100 |
| Females % Dead..... | 7 | 32 | 46 | 58 | 79 | 90 | * 98 |

*Last female died on 49th day.

flies from *all* cages as they died, rather than by individual cage.

Inasmuch as these flies had been maintained on sugar and water only, the further possibility existed that the observed shorter male longevity might be the result of dietary deficiency unilaterally affecting the male. This resulted in a third, more extensive study (experiment 3) to determine the possible role of diet in the differential longevities between sexes of this species. This consisted of two sets of two cages each (containing a total of about 700 flies of both sexes per set) one set being supplied with sugar and water only, the second with sugar, water and Klim, ad libitum. All other conditions of maintenance were identical with those of earlier studies. The study (experiment 4) was repeated with two similar sets of two cages each (containing 500 flies of both sexes per set). Dead flies were periodically collected, pooled, and counted, as before, for each set, until the last fly died.

Finally, the possible effect of parental age at the time of oviposition upon the longevity of offspring was studied in an initial, preliminary experiment involving about 200-250 offspring in each case. Eggs were collected at parental age of 4 days to 27 days. All the flies were maintained on a complete diet of sugar, water, and Klim and under otherwise identical conditions as described above.

## RESULTS

Table 1, experiment 1, shows the results of the study in which only surviving flies were counted. An initial sex ratio of one female to one male at 24 hours rose sharply to two to one at about two weeks and to over three to one by the nineteenth day. The data of experiment 2 (table 2) are more especially significant in showing that, by the second week, the mortality rate of male flies increased very rapidly, so that by the third week two-thirds of the males (in contrast to only one-third of the females) were dead. However, by the fourth week, the female mortality rate began to accelerate so that by the end of the fifth week (when 99 per cent of the males were dead), 90 per cent of the females had also died. Nevertheless, the last female outlived the last male by about a week under these conditions. Thus even with

TABLE 3. EFFECT OF DIET ON LONGEVITY OF HOUSE FLIES.

Per cent Mortality

| | Experiment 3 | | | | Experiment 4 | | | |
|---|---|---|---|---|---|---|---|---|
| | With Klim | | Sugar and Water only | | With Klim | | Sugar and Water only | |
| Age in Days | (366) Males % | (322) Females % | (338) Males % | (349) Females % | (251) Males % | (260) Females % | (229) Males % | (261) Females % |
| 14 | 39 | 7 | 47 | 14 | 60 | 11 | 52 | 19 |
| 21 | 79 | 20 | 92 | 73 | 88 | 24 | 91 | 62 |
| 28 | 90 | 33 | 98 | 95 | 96 | 38 | 99 | 94 |
| 35 | 98 | 58 | 99 | 98 | 98 | 62 | 100 | 100 |
| 42 | 99 | 83 | 100 | 99 | 100 | 85 | Last Male 29 days Last Female 35 days | |
| 49 | 100 | 94 | ..... | 100 | ..... | 96 | | |
| 56 | ..... | 97 | Last Male 40 days Last Female 50 days | | ..... | 100 | | |
| 63 | ..... Last Male 44 days Last Female 64 days | 99 | | | Last Male 40 days Last Female 56 days | | | |

a limited diet of sugar and water, female average and maximum longevities are considerably greater than those of male house flies.

Studies on the effect of different diets on the longevity of house flies are shown in table 3. Numbers in parentheses placed above the columns entitled "Males" and "Females" represent initial populations of each sex for each designated diet. It is obvious that the original sex ratios, based on the usual, random collection of eggs of approximately equal numbers, were very close to one to one. It is further noteworthy that the shorter average and maximum longevities of male flies were not altered by improvement of the diet with Klim (with a butterfat content of 28 per cent, 27 per cent protein, and 3 per cent mineral). Thus, as before, about 90 per cent of the males had died by the fourth week, with or without Klim. Females, on the contrary, showed a 20-25 per cent mortality at 21 days for a diet enriched with Klim, in contrast to a 60-70 per cent mortality for females maintained on sugar and water alone. Again, at 5 weeks, only 60 per cent of the females were dead for cages containing Klim, in contrast to almost 100 per cent at the end of the same period for females maintained on sugar and water alone. In addition, the maximum female longevity seems to be extended by about two weeks by the enriched diet.

In table 4 the longevity data for males and females under the contrasting conditions of diet are summarized.

The results of the investigation concerning the possible effect of parental age at the time of oviposition upon the longevity of offspring are shown in table 5, and are based on 50 per cent mortality time for females (i.e., 30 days) from very young parents (4 days of age) on an enriched diet. It is readily noticeable that male mortalities were not affected significantly by the age of the parents at the time of egg-laying of this $F_1$ generation. By the same criterion, however, female longevity continued to be reduced as the age of the parents at oviposition time was increased; thus, for parents 27 days of age, female offspring mortality was reduced to a point where it was virtually identical with that of the males at 30 days (regardless of age of parents or diet of the aging male flies).

TABLE 4. EFFECT OF DIET ON LONGEVITY OF MALE AND FEMALE HOUSE FLIES.

| | Experiment 3 | | | | Experiment 4 | | | |
|---|---|---|---|---|---|---|---|---|
| | With Klim | | Sugar and Water only | | With Klim | | Sugar and Water only | |
| | Males | Females | Males | Females | Males | Females | Males | Females |
| Average Longevity (Days) | 17.5 | 32.7 | 15.6 | 19.5 | 14.4 | 30.8 | 14.6 | 19.7 |
| Maximum Longevity (Days) | 44 | 64 | 40 | 50 | 40 | 56 | 29 | 35 |

TABLE 5. EFFECT OF PARENTAL AGE ON OFFSPRING LONGEVITY.

| Parental Age (Days) | Per cent Mortality at 30 Days | |
|---|---|---|
| | Males | Females |
| 4 | 95 | 50 |
| 6 | 93 | 52 |
| 9 | 97 | 70 |
| 15 | 92 | 82 |
| 23 | 97 | 80 |
| 27 | 90 | 92 |

## DISCUSSION

Even under suboptimal conditions, the maximal longevity of the female house fly is at least 25 per cent greater than that of the male and about 50 per cent greater under more favorable dietary conditions; in actual days this is about a week and 20 days, respectively. From table 4, which represents a summary of the data of table 3, as well as of calculations of average longevities for this particular study, it is strikingly apparent that the average male longevity of about 15 days (irrespective of dietary changes, which *do* affect female longevity) and a maximum lifespan of about 40 days are relatively immutable; as table 4 also clearly shows, these are also independent of parental age at the time of egg-laying. Female offspring, on the other hand, not only respond favorably to a more complete diet, in terms of heightened longevity, but also show a greater longevity when reared from eggs from very young than those from very old parents. Thus the female longevity (or aging) factor is considerably more labile as far as these two variables of diet and

parental age at oviposition are concerned, in contrast to the refractory nature of the male factor.

Data cited by Hamilton (3) on comparative longevities of male and female members of 70 species of invertebrate and vertebrate animals (a considerable number of which cases are poorly or inadequately documented) show a longer female lifespan for 62 species. Those presented for *Drosophila melanogaster* are probably most significant in terms of controlled diet and size of populations studied. For the wild strain of "fruit flies" he quotes an average longevity of 33 days for the female and about 30 days for the male. However, females of the vestigial wing strain had a longer duration of life (than the male), even greater than in normal flies. In the honey bee, under field and laboratory conditions, this writer can confirm figures given by other observers (10) of a maximum longevity of about 10 months for the female (worker) as against about 6 months for the male (drone). As for mammals, data cited by Hamilton for the white mouse indicates practically no significant difference between male and female longevities, whereas those for female rats are significantly higher than for males. Under excellent conditions of breeding, rearing, and maintenance, male albino rats have longevities of up to 800 days, in contrast to female longevities of up to 1,000 days, in the Laboratory of Dr. Henry Simms of the Columbia University College of Physicians and Surgeons (1). Recent authoritative statistics (2) on human longevities in the United States place female life expectancy at 72 years and that of males at 66 years of age.

The preliminary findings of greater longevities for female house flies reared from eggs laid by very young in contrast to those from very old parents raises the question as to the precise nature of this relatively labile aging (or longevity) factor of the female house flies. The now-classical study of Lansing (4, 5) establishing the presence of a cumulative, reversible, nongenic factor in parthenogenetically-produced offspring has suggested the plan of attack on the aging factor in house flies. Because this involves offspring from fertilized eggs in a bisexual animal species, significant clues as to the possible role of parental age in aging of other bisexual animals, including mammals, may be obtained from such a study now in progress in the writer's laboratory to determine if the female house fly aging factor is cumulative and/or reversible.

SUMMARY

The relative longevities of male and female house flies, *Musca domestica* L., were studied under controlled laboratory conditions of temperature, humidity, and diet. At 80 F. and 45 per cent relative humidity, male house flies showed a lower average and maximum longevity than females even under limited dietary conditions. Under conditions of optimal diet (sugar, water, and powdered whole milk) male longevities of about 15 days and maxima of about 40 days were immutable. Female average longevities, on the other hand, were increased from about 20 days to about 32 days, and female maximum longevities from about 45-50 days to about 60 days by the addition of powered whole milk to the original diet of sugar and water. In a similar fashion, female longevity could be reduced by selecting eggs from very old parents, whereas the male longevity was unaffected by such selection.

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# PROLONGATION OF THE NORMAL LIFE SPAN BY RADIATION PROTECTION CHEMICALS

DENHAM HARMAN, M.D., Ph.D.
*(From the Donner Laboratory, University of California, Berkeley)*

The theory (1) has been advanced that aging may be due in part to the deleterious side effects of the free radicals produced in the normal course of metabolism. In such a system it would be suspected that HO or $HO_2$ radicals are chiefly responsible; these would be expected to arise for the most part in the interaction of oxidative enzymes with oxygen or by the action of catalase on hydrogen peroxide.

On the basis of this theory, it would be anticipated that raising the concentration in the organism of compounds, such as cysteine and other radiation protection chemicals capable of reacting rapidly with free radicals, would tend to slow down the aging process and thus lead to an extension of the normal life span. This possibility has been tested in the past year. Two strains of mice were employed; the AKR mice (males) and C3H mice (females) which develop spontaneous lymphatic leukemia and mammary carcinoma, respectively. These mice were used because their life is relatively short. Although they die of lymphatic leukemia or carcinoma, it was believed that they should be suitable for testing the proposed aging theory since, if it is correct, the average age at which the neoplastic process appeared might be increased.

## MATERIAL AND METHODS

AKR (males) and C3H (females) mice were obtained from the Jackson Memorial Laboratory of Bar Harbor, Maine, immediately after weaning. They were fed ad lib with a powdered diet to which had been added, with the exception of the controls, one of a number of reducing agents: 1) cysteine hydrochloride, 2) ascorbic acid, 3) 2-mercaptoethylamine hydrochloride, 4) 2,2′-diaminodiethyl disulfide dihydrochloride, and 5) 2-mercaptoethanol. These were mixed in the powdered meal by first dissolving the chemical in a little water and then spraying it over the meal spread out on a clean, flat surface. After thorough mixing, the food was placed in 8 × 4 cm. crystallizing dishes and then placed in the cages. The food was prepared fresh each day.

Initially 30 mice were employed at each concentration for each chemical evaluated. The effective number of mice was less than this due to several causes; for example, some mice were sacrificed for gross pathologic studies (no effects of the chemicals were noted) while others managed to get out of their cages and hence were discarded. A couple of months after the experiment was started more mice were obtained as controls because a number in the original group had been inadvertently lost. These new control animals were kept on a pellet diet rather than on powdered food. As will be noted below, the life span of these mice was the same as those on powdered food. The only significant difference between the two groups was the weight; those on powdered food were heavier. The death rate of the AKR controls was essentially the same as that obtained in the laboratory from which they were obtained (Jackson Memorial Laboratory in Bar Harbor, Maine). However, the life span of the C3H mice was greater than that noted at the Jackson Memorial Laboratory; this difference is attributed to the fact that the present controls were virgins, while those employed for the life span studies at the Jackson Memorial Laboratory were breeders (2).

Each month the average weight of the mice in each cage was determined by weighing them together and then dividing their total weight by the number of mice. After the experiment had been in progress 6 months, the AKR mice that died each day were autopsied, and it was noted whether or not the dead C3H mice had tumors. With very rare exception all the AKR mice were found to have leukemia as evidenced by large spleens and lymph nodes at autopsy. Likewise almost all the dead C3H mice had tumors.

On two occasions, blood smears were taken (at 12-13 months of age) from the AKR mice

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TABLE 1-A. AKR MICE. EFFECT OF ANTIOXIDANTS ON THEIR LIFE SPAN. Complete Mortality Data.

| Age, Months | Controls | | | | | | | | | Cysteine Hydrochloride | | | | | | | | Ascorbic Acid | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Bar Harbor | Pellets | | | | Powder | | | | 0.5% | | | | 1.0% | | | | 2.0% | | | |
| | L* | B5 L | B6 L | B7 L | Σ L | C13 L | C14 L | C15 L | Σ L | C1 L | C2 L | C3 L | Σ L | C4 L | C5 L | C6 L | Σ L | C22 L | C23 L | C24 L | Σ L |
| 1.0 | 56 | 11 | 11 | 10 | 32 | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — |
| 1.5 | — | — | — | — | — | 8 | 10 | 8 | 26 | 10 | 10 | 10 | 30 | 10 | 10 | 10 | 30 | — | — | — | — |
| 2.0 | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — |
| 2.5 | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | 9† | 10 | 10 | 29 |
| 3.0 | — | — | — | — | — | 7† | 9 | 7 | 23 | 10 | 9 | 10 | 29 | 10 | 10 | 9† | 29 | — | — | — | — |
| 4.0 | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — |
| 4.5 | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | 7 | 9† | 8 | 24 |
| 5.0 | 51 | — | — | — | — | 5 | 8 | 5 | 18 | 10 | 8† | 10 | 28 | 9 | 10 | 7 | 26 | — | — | — | — |
| 5.5 | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — |
| 6.0 | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — |
| 6.5 | 35 | 8 | 6 | 6 | 20 | — | — | — | — | — | — | — | — | — | — | — | — | 3 | 8 | 6 | 17 |
| 7.0 | — | — | — | — | — | 3 | 6 | 5 | 14 | 9 | 8 | 7 | 24 | 6 | 10 | 7 | 23 | — | — | — | — |
| 7.5 | — | 7 | 6 | 4 | 17 | — | — | — | — | — | — | — | — | — | — | — | — | 2 | 7 | 5 | 14 |
| 8.0 | — | — | — | — | — | 3 | 5† | 5 | 13 | 8† | 6 | 5 | 19 | 6 | 8† | 7 | 21 | — | — | — | — |
| 8.5 | 17 | 6 | 6 | 2 | 14 | — | — | 2 | — | — | — | — | — | — | — | — | — | 2 | 4 | 4 | 10 |
| 9.0 | — | — | — | — | — | 2 | 4 | 0 | 6 | 5 | 5 | 2 | 12 | 6 | 7 | 7 | 20 | — | — | — | — |
| 9.5 | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | 0 | 3 | 3 | 6 |
| 10.0 | 8 | 4 | 3 | 1 | 8 | 0 | 2 | — | 2 | 4 | 4 | 2 | 10 | 5 | 5 | 7 | 17 | — | — | — | — |
| 10.5 | — | 3 | 3 | 1 | 7 | — | — | — | — | — | — | — | — | — | — | — | — | — | 3 | 3 | 6 |
| 11.0 | — | — | — | — | — | — | 2 | — | 2 | 4 | 4 | 1 | 9 | 3 | 4 | 6 | 13 | — | — | — | — |
| 11.5 | 2 | 2 | 3 | 1 | 6 | — | — | — | — | — | — | — | — | — | — | — | — | — | 2 | 2 | 4 |
| 12.0 | — | — | — | — | — | — | 2 | — | 2 | 3 | 4 | 0 | 7 | 3 | 3 | 4 | 10 | — | — | — | — |
| 12.5 | — | 2 | 3 | 1 | 6 | — | — | — | — | — | — | — | — | — | — | — | — | — | 2 | 2 | 4 |
| 13.0 | — | — | — | — | — | — | 2 | — | 2 | 2 | 2 | — | 4 | 2 | 3 | 2 | 7 | — | — | — | — |
| 13.5 | 1 | 1 | 3 | 0 | 4 | — | — | — | — | — | — | — | — | — | — | — | — | — | 1 | 1 | 2 |
| 14.0 | — | — | — | — | — | — | 2 | — | 2 | 1 | 1 | — | 2 | 2 | 1 | 1 | 4 | — | — | — | — |
| 14.5 | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | 1 | 1 | 2 |
| 15.0 | — | — | — | — | — | — | 1 | — | 1 | 1 | 1 | — | 2 | 2 | 0 | 1 | 3 | — | — | — | — |
| 15.5 | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | 1 | 1 | 2 |
| 16.0 | — | — | — | — | — | — | 1 | — | 1 | 0 | 1 | — | 1 | 2 | — | 1 | 3 | — | — | — | — |

* = Living. † Taken for autopsy—one mouse.

TABLE 1-B. AKR MICE. EFFECT OF ANTIOXIDANTS ON THEIR LIFE SPAN. Complete Mortality Data.

| Age, Months | 2—Mercaptoethylamine Hydrochloride | | | | | | | | 2, 2′—Diaminodiethyl Disulfide Dihydrochloride | | | | | | | | 2—Mercaptoethanol | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 0.5% | | | | 1.0% | | | | 0.5% | | | | 1.0% | | | | 0.5% | | | |
| | C31 L* | C32 L | C33 L | Σ L | C34 L | C35 L | C36 L | Σ L | C43 L | C44 L | C45 L | Σ L | C46 L | C47 L | C48 L | Σ L | C19 L | C20 L | C21 L | Σ L |
| 1.0 | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | 9† | — | — | — |
| 1.5 | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — |
| 2.0 | 10 | 10 | 10 | 30 | 10 | 10 | 4 | 24 | 10 | 10 | 10 | 30 | 9 | 6 | 10 | 25 | — | — | — | — |
| 2.5 | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | 8 | 9 | 9 | 26 |
| 3.0 | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — |
| 3.5 | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — |
| 4.0 | 9† | 9 | 9† | 27 | 10 | 8† | 4 | 22 | 9† | 8 | 8 | 27 | 8† | 3 | 10 | 21 | — | — | — | — |
| 4.5 | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | 7 | 7† | 6 | 20 |
| 5.0 | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — |
| 5.5 | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — |
| 6.0 | 7 | 8 | 6 | 21 | 9 | 8 | 4 | 21 | 9 | 7 | 8 | 24 | 8 | 1 | 7 | 16 | — | — | — | — |
| 6.5 | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | 7 | 6 | 3 | 16 |
| 7.0 | 7 | 8 | 3 | 18 | 9 | 7† | 4 | 20 | 8† | 7 | 8 | 23 | 7 | 1 | 7 | 15 | — | — | — | — |
| 7.5 | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | 7 | 4 | 3 | 14 |
| 8.0 | 7 | 7 | 1 | 15 | 8 | 6 | 4 | 18 | 7 | 7 | 8 | 22 | 4 | 1 | 6 | 11 | — | — | — | — |
| 8.5 | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | 6 | 2 | 3 | 11 |
| 9.0 | 5 | 5 | 1 | 11 | 7 | 6 | 2 | 15 | 7 | 7 | 7 | 21 | 4 | 0 | 3 | 7 | — | — | — | — |
| 9.5 | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | 6 | 2 | 2 | 10 |
| 10.0 | 3 | 3 | 0 | 6 | 5 | 6 | 1 | 12 | 7 | 5 | 7 | 19 | 2 | — | 3 | 5 | — | — | — | — |
| 10.5 | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | 4 | 1 | 2 | 7 |
| 11.0 | 2 | 3 | — | 5 | 5 | 4 | 1 | 10 | 6 | 3 | 3 | 12 | 2 | — | 3 | 5 | — | — | — | — |
| 11.5 | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | 3 | 1 | 2 | 6 |
| 12.0 | 0 | 3 | — | 3 | 2 | 3 | 0 | 5 | 5 | 2 | 2 | 9 | 0 | — | 2 | 2 | — | — | — | — |
| 12.5 | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | 3 | 0 | 2 | 5 |
| 13.0 | — | 2 | — | 2 | 1 | 2 | — | 3 | 2 | 1 | 2 | 5 | — | — | 1 | 1 | — | — | — | — |
| 13.5 | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | 3 | — | 1 | 4 |
| 14.0 | — | 0 | — | 0 | 0 | 2 | — | 2 | 1 | 0 | 2 | 3 | — | — | 1 | 1 | — | — | — | — |
| 14.5 | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | 2 | — | 0 | 2 |
| 15.0 | — | — | — | — | — | 1 | — | 1 | 1 | — | 2 | 3 | — | — | 1 | 1 | — | — | — | — |
| 15.5 | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | 1 | — | — | 1 |
| 16.0 | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — |

* L = Living. † Taken for autopsy—one mouse.

TABLE 2-A. C3H MICE. EFFECT OF ANTIOXIDANTS ON THEIR LIFE SPAN. Complete Mortality Data.

| Age, Months | Bar Harbor | Controls | | | | | | | | | | | | Cysteine Hydrochloride | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Pellets | | | | | | | | | Powder | | | | | 0.5% | | | | | | 1.0% | | | |
| | | B1 | | B2 | | B3 | | B4 | | Σ | | C16 | | C17 | | C18 | | Σ | | C7 | | C8 | | C9 | | Σ | |
| | L* | L | T† | L | T | L | T | L | T | L | T | L | T | L | T | L | T | L | T | L | T | L | T | L | T | L | T |
| 1.0 | 247 | 8 | 0 | 9 | 0 | 10 | 0 | 10 | 0 | 37 | 0 | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — |
| 1.5 | — | — | — | — | — | — | — | — | — | — | — | 10 | 0 | 8 | 0 | 4 | 0 | 22 | 0 | 9 | 0 | 10 | 0 | 10 | 0 | 29 | 0 |
| 2.0 | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — |
| 2.5 | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — |
| 3.0 | — | — | — | — | — | — | — | — | — | — | — | 9‡ | 0 | 8 | 0 | 4 | 0 | 21 | 0 | 8‡ | 0 | 10 | 0 | 10 | 0 | 29 | 0 |
| 3.5 | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — |
| 4.0 | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — |
| 4.5 | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — |
| 5.0 | 231 | — | — | — | — | — | — | — | — | — | — | 9 | 0 | 8 | 0 | 4 | 0 | 21 | 0 | 8 | 0 | 10 | 0 | 10 | 0 | 28 | 0 |
| 5.5 | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — |
| 6.0 | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — |
| 6.5 | 206 | 8 | 0 | 9 | 1 | 10 | 0 | 10 | 0 | 37 | 1 | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — |
| 7.0 | — | — | — | — | — | — | — | — | — | — | — | 9 | 0 | 8 | 0 | 3‡ | 0 | 20 | 0 | 8 | 0 | 10 | 0 | 10 | 1 | 28 | 1 |
| 7.5 | — | 8 | 0 | 8 | 0 | 8‡ | 0 | 10 | 0 | 34 | 0 | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — |
| 8.0 | — | — | — | — | — | — | — | — | — | — | — | 9 | 0 | 8 | 0 | 3 | 0 | 20 | 0 | 7 | 1 | 10 | 0 | 10 | 1 | 27 | 2 |
| 8.5 | 145 | 8 | 2 | 8 | 0 | 8 | 1 | 10 | 0 | 34 | 3 | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — |
| 9.0 | — | — | — | — | — | — | — | — | — | — | — | 9 | 0 | 7 | 0 | 3 | 0 | 19 | 0 | 6 | 2 | 10 | 1 | 9 | 0 | 25 | 3 |
| 9.5 | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — |
| 10.0 | 64 | 7 | 2 | 8 | 0 | 8 | 3 | 10 | 1 | 33 | 6 | 9 | 0 | 7 | 2 | 2 | 2 | 18 | 4 | 5 | 3 | 8‡ | 3 | 9 | 0 | 22 | 6 |
| 10.5 | — | 6 | 2 | 7 | 3 | 8 | 4 | 10 | 1 | 31 | 10 | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — |
| 11.0 | — | — | — | — | — | — | — | — | — | — | — | 9 | 2 | 6 | 2 | 1 | 1 | 16 | 5 | 3 | 1 | 7 | 3 | 8 | 0 | 18 | 4 |
| 11.5 | 21 | 6 | 2 | 8 | 2 | 6 | 4 | 9 | 1 | 29 | 9 | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — |
| 12.0 | — | — | — | — | — | — | — | — | — | — | — | 9 | 4 | 5 | 2 | 1 | 1 | 15 | 7 | 2 | 0 | 5 | 2 | 8 | 1 | 15 | 3 |
| 12.5 | — | 5 | 3 | 5 | 0 | 5 | 3 | 8 | 1 | 23 | 7 | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — |
| 13.0 | — | — | — | — | — | — | — | — | — | — | — | 8 | 5 | 5 | 2 | 1 | 1 | 14 | 8 | 2 | 1 | 4 | 4 | 7 | 1 | 13 | 6 |
| 13.5 | 9 | 2 | 0 | 5 | 2 | 5 | 4 | 8 | 4 | 20 | 10 | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — |
| 14.0 | — | — | — | — | — | — | — | — | — | — | — | 7 | 5 | 5 | 4 | — | — | 12 | 9 | 2 | 1 | 4 | 4 | 7 | 3 | 13 | 8 |
| 14.5 | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — |
| 15.0 | — | — | — | — | — | — | — | — | — | — | — | 5 | 3 | 4 | 4 | — | — | 9 | 7 | 1 | 1 | 2 | 2 | 6 | 2 | 9 | 5 |
| 15.5 | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — |
| 16.0 | — | 2 | 2 | 3 | 0 | 1 | 0 | 0 | 0 | 6 | 2 | 3 | 1 | 1 | 1 | — | — | 4 | 2 | 1 | 1 | 1 | 1 | 5 | 2 | 7 | 4 |

| Age, Months | Cysteine Hydrochloride | | | | | | | | Ascorbic Acid | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 1.0% | | | | | | | | 2.0% | | | | | | | |
| | C10 | | C11 | | C12 | | Σ | | C28 | | C29 | | C30 | | Σ | |
| | L | T | L | T | L | T | L | T | L* | T† | L | T | L | T | L | T |
| 1.0 | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — |
| 1.5 | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — |
| 2.0 | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — |
| 2.5 | — | — | — | — | — | — | — | — | 10 | 0 | 9 | 0 | 10 | 0 | 29 | 0 |
| 3.0 | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — |
| 3.5 | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — |
| 4.0 | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — |
| 4.5 | — | — | — | — | — | — | — | — | 9‡ | 0 | 9 | 0 | 10 | 0 | 28 | 0 |
| 5.0 | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — |
| 5.5 | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — |
| 6.0 | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — |
| 6.5 | — | — | — | — | — | — | — | — | 9 | 0 | 9 | 0 | 9 | 0 | 27 | 0 |
| 7.0 | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — |
| 7.5 | — | — | — | — | — | — | — | — | 9 | 0 | 9 | 0 | 9 | 0 | 27 | 0 |
| 8.0 | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — |
| 8.5 | — | — | — | — | — | — | — | — | 9 | 0 | 9 | 0 | 9 | 0 | 27 | 0 |
| 9.0 | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — |
| 9.5 | — | — | — | — | — | — | — | — | 9 | 1 | 9 | 1 | 9 | 2 | 27 | 4 |
| 10.0 | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — |
| 10.5 | — | — | — | — | — | — | — | — | 8 | 0 | 9 | 2 | 8 | 3 | 25 | 5 |
| 11.0 | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — |
| 11.5 | — | — | — | — | — | — | — | — | 7 | 4 | 7 | 4 | 6 | 5 | 20 | 13 |
| 12.0 | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — |
| 12.5 | — | — | — | — | — | — | — | — | 4 | 3 | 6 | 4 | 6 | 5 | 16 | 12 |
| 13.0 | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — |
| 13.5 | — | — | — | — | — | — | — | — | 4 | 4 | 5 | 3 | 4 | 3 | 13 | 10 |
| 14.0 | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — |
| 14.5 | — | — | — | — | — | — | — | — | 3 | 3 | 4 | 2 | 2 | 1 | 9 | 6 |
| 15.0 | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — |
| 15.5 | — | — | — | — | — | — | — | — | 2 | 2 | 2 | 0 | 1 | 0 | 5 | 2 |
| 16.0 | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — |

| Age, Months | 2—Mercaptoethylamine Hydrochloride | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 0.5% | | | | | | | | 1.0% | | | | | | | |
| | C37 | | C38 | | C39 | | Σ | | C40 | | C41 | | C42 | | Σ | |
| | L | T | L | T | L | T | L | T | L | T | L | T | L | T | L | T |
| 1.0 | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — |
| 1.5 | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — |
| 2.0 | 10 | 0 | 10 | 0 | 10 | 0 | 30 | 0 | 10 | 0 | 10 | 0 | 9 | 0 | 29 | 0 |
| 2.5 | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — |
| 3.0 | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — |
| 3.5 | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — |
| 4.0 | 9‡ | 0 | 10 | 0 | 10 | 0 | 29 | 0 | 10 | 0 | 9† | 0 | 9 | 0 | 28 | 0 |
| 4.5 | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — |
| 5.0 | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — |
| 5.5 | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — |
| 6.0 | 9 | 0 | 10 | 0 | 10 | 0 | 29 | 0 | 8‡ | 0 | 9 | 0 | 9 | 0 | 26 | 0 |
| 6.5 | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — |
| 7.0 | 9 | 0 | 10 | 1 | 9§ | 0 | 28 | 1 | 8 | 0 | 8† | 1 | 9 | 0 | 25 | 1 |
| 7.5 | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — |
| 8.0 | 9 | 0 | 10 | 3 | 9 | 0 | 28 | 3 | 8 | 1 | 8 | 1 | 9 | 0 | 25 | 2 |
| 8.5 | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — |
| 9.0 | 9 | 0 | 8 | 1 | 9 | 0 | 26 | 1 | 7 | 0 | 7 | 1 | 9 | 0 | 23 | 1 |
| 9.5 | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — |
| 10.0 | 9 | 2 | 8 | 1 | 9 | 1 | 26 | 4 | 7 | 0 | 7 | 2 | 9 | 0 | 23 | 2 |
| 10.5 | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — |
| 11.0 | 9 | 3 | 7 | 3 | 9 | 2 | 25 | 7 | 7 | 0 | 6 | 2 | 9 | 1 | 22 | 3 |
| 11.5 | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — |
| 12.0 | 8 | 5 | 7 | 4 | 9 | 4 | 24 | 13 | 7 | 1 | 4 | 0 | 9 | 2 | 20 | 3 |
| 12.5 | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — |
| 13.0 | 4 | 1 | 5 | 2 | 7 | 2 | 16 | 5 | 7 | 5 | 4 | 1 | 8 | 3 | 19 | 9 |
| 13.5 | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — |
| 14.0 | 3 | 1 | 5 | 4 | 5 | 1 | 13 | 6 | 5 | 4 | 4 | 2 | 6 | 1 | 15 | 7 |
| 14.5 | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — |
| 15.0 | 2 | 1 | 3 | 3 | 4 | 0 | 9 | 4 | 4 | 3 | 3 | 1 | 2 | 1 | 9 | 5 |
| 15.5 | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — |
| 16.0 | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — |

* L = Living. † T = Number of mice with tumors. ‡ = Two died from lack of water. § = Taken for autopsy—one mouse.

TABLE 2-B. C3H MICE. EFFECT OF ANTIOXIDANTS ON THEIR LIFE SPAN. Complete Mortality Data.

* L = Living. † T = Number of mice with tumors. ‡ = Two died in water bottle. § = Taken for autopsy—one mouse.

TABLE 2-C. C3H MICE. EFFECT OF ANTIOXIDANTS ON THEIR LIFE SPAN. Complete Mortality Data.

| Age, Months | 2, 2'—Diaminodiethyl Disulfide Dihydrochloride | | | | | | | | | | | | | | | | 2—Mercaptoethanol | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 0.5% | | | | | | | | 1.0% | | | | | | | | 0.5% | | | | | | | |
| | C49 | | C50 | | C51 | | Σ | | C52 | | C53 | | C54 | | Σ | | C25 | | C26 | | C27 | | Σ | |
| | L* | T† | L | T | L | T | L | T | L | T | L | T | L | T | L | T | L | T | L | T | L | T | L | T |
| 1.0 | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — |
| 1.5 | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — |
| 2.0 | 10 | 0 | 10 | 0 | 9 | 0 | 29 | 0 | 9 | 0 | 10 | 0 | 10 | 0 | 29 | 0 | — | — | — | — | — | — | — | — |
| 2.5 | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | 10 | 0 | 10 | 0 | 8 | 0 | 28 | 0 |
| 3.0 | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — |
| 3.5 | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — |
| 4.0 | 9§ | 0 | 10 | 0 | 9 | 0 | 28 | 0 | 8§ | 0 | 10 | 0 | 10 | 0 | 28 | 0 | — | — | — | — | — | — | — | — |
| 4.5 | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | 9§ | 0 | 6‡ | 0 | 8 | 0 | 23 | 0 |
| 5.0 | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — |
| 5.5 | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — |
| 6.0 | 9 | 0 | 10 | 0 | 9 | 0 | 28 | 0 | 7 | 1 | 10 | 0 | 10 | 0 | 27 | 1 | — | — | — | — | — | — | — | — |
| 6.5 | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | 9 | 0 | 6 | 0 | 8 | 0 | 23 | 0 |
| 7.0 | 8§ | 0 | 10 | 1 | 9 | 0 | 27 | 0 | 6 | 1 | 10 | 0 | 10 | 0 | 26 | 1 | — | — | — | — | — | — | — | — |
| 7.5 | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | 8§ | 0 | 6 | 0 | 8 | 0 | 22 | 0 |
| 8.0 | 8 | 0 | 10 | 2 | 9 | 0 | 27 | 0 | 5 | 0 | 10 | 0 | 10 | 0 | 25 | 0 | — | — | — | — | — | — | — | — |
| 8.5 | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | 8 | 0 | 6 | 0 | 8 | 0 | 22 | 0 |
| 9.0 | 8 | 2 | 9 | 3 | 9 | 2 | 26 | 7 | 5 | 0 | 10 | 1 | 10 | 0 | 25 | 1 | — | — | — | — | — | — | — | — |
| 9.5 | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | 8 | 0 | 6 | 2 | 8 | 0 | 22 | 0 |
| 10.0 | 8 | 2 | 8 | 2 | 8 | 3 | 24 | 7 | 5 | 1 | 10 | 3 | 10 | 0 | 25 | 4 | — | — | — | — | — | — | — | — |
| 10.5 | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | 8 | 0 | 5 | 2 | 8 | 2 | 21 | 4 |
| 11.0 | 8 | 2 | 7 | 1 | 8 | 5 | 23 | 8 | 5 | 1 | 9 | 3 | 8 | 2 | 22 | 6 | — | — | — | — | — | — | — | — |
| 11.5 | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | 8 | 2 | 4 | 2 | 7 | 2 | 19 | 6 |
| 12.0 | 7 | 2 | 7 | 2 | 6 | 3 | 20 | 7 | 5 | 1 | 8 | 5 | 7 | 1 | 20 | 7 | — | — | — | — | — | — | — | — |
| 12.5 | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | 8 | 2 | 4 | 2 | 6 | 2 | 18 | 6 |
| 13.0 | 6 | 2 | 6 | 2 | 5 | 4 | 17 | 8 | 5 | 1 | 7 | 4 | 7 | 3 | 19 | 8 | — | — | — | — | — | — | — | — |
| 13.5 | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | 7 | 4 | 3 | 1 | 6 | 3 | 16 | 8 |
| 14.0 | 6 | 2 | 5 | 1 | 3 | 2 | 14 | 5 | 4 | 3 | 5 | 2 | 6 | 4 | 15 | 9 | — | — | — | — | — | — | — | — |
| 14.5 | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | 6 | 3 | 2 | 2 | 6 | 5 | 14 | 10 |
| 15.0 | 4 | 2 | 5 | 2 | 2 | 2 | 11 | 6 | 3 | 2 | 4 | 4 | 4 | 2 | 11 | 8 | — | — | — | — | — | — | — | — |
| 15.5 | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | 5 | 3 | 1 | 1 | 4 | 4 | 10 | 8 |
| 16.0 | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — |

* L = Living. † T = Number of mice with tumors. ‡ = No record of how these four were lost. § = Taken for autopsy—one mouse.

TABLE 3-A. AKR MICE. EFFECT OF ANTIOXIDANTS ON THEIR LIFE SPAN. Adjusted Mortality Data and Weights.

| Age, Months | Controls | | | | | | | | | Cysteine Hydrochloride | | | | | | Ascorbic Acid | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Bar Harbor | | Pellets | | | Powder | | | | 0.5% | | | 1.0% | | | 2.0% | | |
| | No. Living | % of Start | No. Living | % of Start | Aver. Wt. | No. Living | % of Start | Aver. Wt. | | No. Living | % of Start | Aver. Wt. | No. Living | % of Start | Aver. Wt. | No. Living | % of Start | Aver. Wt. |
| 1.0 | 56 | 100 | 32 | 100 | — | 24 | 100 | — | | 28 | 100 | — | 28 | 100 | — | 27 | 100 | — |
| 1.5 | — | — | — | — | — | — | — | — | | — | — | — | — | — | — | — | — | — |
| 2.0 | — | — | — | — | — | — | — | — | | — | — | — | — | — | — | — | — | — |
| 2.5 | — | — | — | — | — | — | — | — | | — | — | — | — | — | — | 27 | 100 | 23.0 |
| 3.0 | — | — | — | — | — | 22 | 92.0 | 24.9 | | 27 | 96.3 | 21.9 | 28 | 100 | 22.6 | — | — | — |
| 3.5 | — | — | — | — | — | — | — | — | | — | — | — | — | — | — | — | — | — |
| 4.0 | — | — | — | — | — | — | — | — | | — | — | — | — | — | — | — | — | — |
| 4.5 | — | — | — | — | — | — | — | — | | — | — | — | — | — | — | 24 | 89.0 | 30.0 |
| 5.0 | 51 | 91.2 | — | — | — | 17 | 71.0 | 30.8 | | 27 | 96.3 | 30.2 | 25 | 89.5 | 29.3 | — | — | — |
| 5.5 | — | — | — | — | — | — | — | — | | — | — | — | — | — | — | — | — | — |
| 6.0 | — | — | — | — | — | — | — | — | | — | — | — | — | — | — | — | — | — |
| 6.5 | 35 | 62.5 | 20 | 62.5 | 30.3 | — | — | — | | — | — | — | — | — | — | 17 | 63.0 | 3.17 |
| 7.0 | — | — | — | — | — | 13 | 54.2 | 32.1 | | 23 | 82.3 | 31.9 | 22 | 78.6 | 31.9 | — | — | — |
| 7.5 | — | — | 17 | 53.5 | 32.9 | — | — | — | | — | — | — | — | — | — | 14 | 57.8 | 31.9 |
| 8.0 | — | — | — | — | — | 13 | 54.2 | 32.4 | | 19 | 68.0 | 32.9 | 21 | 75.0 | 33.3 | — | — | — |
| 8.5 | 17 | 30.3 | 14 | 43.7 | 34.3 | — | — | — | | — | — | — | — | — | — | 10 | 37.0 | 32.2 |
| 9.0 | — | — | — | — | — | 6 | 25.0 | 30.3 | | 12 | 42.8 | 33.8 | 20 | 71.5 | 33.4 | — | — | — |
| 9.5 | — | — | — | — | — | — | — | — | | — | — | — | — | — | — | 6 | 22.2 | 35.7 |
| 10.0 | 8 | 14.3 | 8 | 25.0 | 33.7 | 2 | 8.3 | 39.0 | | 10 | 35.8 | 36.0 | 17 | 60.8 | 32.8 | — | — | — |
| 10.5 | — | — | 7 | 21.8 | 31.5 | — | — | — | | — | — | — | — | — | — | 6 | 22.2 | 33.2 |
| 11.0 | — | — | — | — | — | 2 | 8.3 | 40.5 | | 9 | 31.1 | 36.9 | 13 | 46.4 | 34.4 | — | — | — |
| 11.5 | 2 | 3.6 | 5 | 15.5 | 34.4 | — | — | — | | — | — | — | — | — | — | 4 | 14.8 | 34.0 |
| 12.0 | — | — | — | — | — | 2 | 8.3 | 40.0 | | 7 | 25.0 | 38.0 | 10 | 35.8 | 33.1 | — | — | — |
| 12.5 | — | — | 5 | 15.5 | 30.2 | — | — | — | | — | — | — | — | — | — | 4 | 14.8 | 32.7 |
| 13.0 | — | — | — | — | — | 2 | 8.3 | 41.0 | | 4 | 14.3 | 36.5 | 7 | 25.0 | 32.5 | — | — | — |
| 13.5 | 1 | 1.8 | 3 | 9.4 | 29.7 | — | — | — | | — | — | — | — | — | — | 2 | 7.4 | 40.5 |
| 14.0 | — | — | — | — | — | 2 | 8.3 | 41.0 | | 2 | 7.1 | 33.5 | 4 | 14.2 | 36.2 | — | — | — |
| 14.5 | — | — | — | — | — | — | — | — | | — | — | — | — | — | — | 2 | 7.4 | 36.0 |
| 15.0 | — | — | — | — | — | 1 | 4.2 | 43.0 | | 2 | 7.1 | 29.5 | 3 | 10.1 | 37.0 | — | — | — |
| 15.5 | — | — | — | — | — | — | — | — | | — | — | — | — | — | — | — | — | — |

TABLE 3-B. AKR MICE. EFFECT OF ANTIOXIDANTS ON THEIR LIFE SPAN. Adjusted Mortality Data and Weights.

| Age, Months | 2—Mercaptoethylamine Hydrochloride 0.5% No. Living | % of Start | Aver. Wt. | 1.0% No. Living | % of Start | Aver. Wt. | 2, 2'—Diaminodiethyl Disulfide Dihydrochloride 0.5% No. Living | % of Start | Aver. Wt. | 1 .0% No. Living | % of Start | Aver. Wt. | 2—Mercaptoethanol 0.5% No. Living | % of Start | Aver. Wt. |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1.0 | 28 | 100 | — | 22 | 100 | — | 28 | 100 | — | 24 | 100 | — | 25 | 100 | — |
| 1.5 | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — |
| 2.0 | 28 | 100 | 20.8 | 22 | 100 | 21.4 | 28 | 100 | 20.9 | 24 | 100 | 25.5 | — | — | — |
| 2.5 | — | — | — | — | — | — | — | — | — | — | — | — | 24 | 95 | 23.9 |
| 3.0 | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — |
| 3.5 | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — |
| 4.0 | 26 | 92.6 | 28.2 | 22 | 100 | 29.4 | 24 | 86.0 | 29.7 | — | 83.3 | 28.2 | — | — | — |
| 4.5 | — | — | — | — | — | — | — | — | — | — | — | — | 19 | 76 | 28.7 |
| 5.0 | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — |
| 5.5 | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — |
| 6.0 | 21 | 75.0 | 31.7 | 20 | 91 | 31.2 | 23 | 82.3 | 31.3 | 15 | 62.5 | 30.5 | — | — | — |
| 6.5 | — | — | — | — | — | — | — | — | — | — | — | — | 15 | 60 | 29.8 |
| 7.0 | 18 | 64.3 | 30.5 | 19 | 86.5 | 30.1 | 23 | 82.3 | 31.4 | 15 | 62.5 | 33.0 | — | — | — |
| 7.5 | — | — | — | — | — | — | — | — | — | — | — | — | 14 | 56 | 27.7 |
| 8.0 | 15 | 53.5 | 31.5 | 18 | 82.0 | 31.1 | 22 | 78.5 | 31.1 | 11 | 45.7 | 33.5 | — | — | — |
| 8.5 | — | — | — | — | — | — | — | — | — | — | — | — | 11 | 44 | 28.3 |
| 9.0 | 11 | 39.4 | 33.8 | 15 | 68.0 | 32.0 | 21 | 75.0 | 30.4 | 7 | 29.1 | 34.1 | — | — | — |
| 9.5 | — | — | — | — | — | — | — | — | — | — | — | — | 10 | 40 | 28.0 |
| 10.0 | 6 | 21.4 | 31.8 | 12 | 54.5 | 32.5 | 19 | 67.7 | 32.1 | 5 | 20.8 | 35.8 | — | — | — |
| 10.5 | — | — | — | — | — | — | — | — | — | — | — | — | 7 | 28 | 30.4 |
| 11.0 | 5 | 17.7 | 29.1 | 10 | 45.4 | 30.7 | 12 | 42.9 | 29.7 | 5 | 20.8 | 29.8 | — | — | — |
| 11.5 | — | — | — | — | — | — | — | — | — | — | — | — | 6 | 24 | 29.2 |
| 12.0 | 3 | 10.7 | 26.7 | 5 | 22.4 | 30.8 | 9 | 32.0 | 29.3 | 2 | 8.3 | 31.0 | — | — | — |
| 12.5 | — | — | — | — | — | — | — | — | — | — | — | — | 5 | 20 | 30.7 |
| 13.0 | 2 | 7.1 | 29.0 | 3 | 13.6 | 33.6 | 5 | 17.8 | 27.4 | 1 | 4.1 | 33.0 | — | — | — |
| 13.5 | — | — | — | — | — | — | — | — | — | — | — | — | 4 | 16 | 30.2 |
| 14.0 | 0 | 0 | — | 2 | 9.1 | 30.0 | 3 | 10.7 | 29.3 | 1 | 4.1 | 33.0 | — | — | — |
| 14.5 | — | — | — | — | — | — | — | — | — | — | — | — | 2 | 8 | 26.0 |
| 15.0 | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — |
| 15.5 | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — |

TABLE 4-A. C3H MICE. EFFECT OF ANTIOXIDANTS ON THEIR LIFE SPAN.† Adjusted Mortality Data and Weights.

| Age, Months | Controls: Bar Harbor Number Living | % of Start | Pellets Number Living | % of Start | Aver. Wt. | No. with Tumors | Powder Number Living | % of Start | Aver. Wt. | No. with Tumors | Cysteine Hydrochloride 0.5% Number Living | % of Start | Aver. Wt. | No. with Tumors | 1.0% Number Living | % of Start | Aver. Wt. | No. with Tumors | Ascorbic Acid 2.0% Number Living | % of Start | Aver. Wt. | No. with Tumors |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1.0 | 247 | 100 | 37 | 100 | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — |
| 1.5 | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — |
| 2.0 | — | — | — | — | — | — | 20 | 100 | — | — | — | — | — | — | — | — | — | — | — | — | — | — |
| 2.5 | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | 28 | 100 | 17.7 | 0 |
| 3.0 | — | — | — | — | — | — | 20 | 100 | 20.5 | 0 | 26 | 100 | 20.6 | 0 | 29 | 100 | 21.2 | 0 | — | — | — | — |
| 3.5 | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — |
| 4.0 | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — |
| 4.5 | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | 28 | 100 | 25.2 | 0 |
| 5.0 | 231 | 93.5 | — | — | — | — | 20 | 100 | 27.0 | 0 | 26 | 100 | 25.5 | 0 | 29 | 100 | 25.3 | 0 | — | — | — | — |
| 5.5 | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — |
| 6.0 | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — |
| 6.5 | 206 | 83.5 | 37 | 100 | 22.8 | 1 | — | — | — | — | — | — | — | — | — | — | — | — | 27 | 96.5 | 25.4 | 0 |
| 7.0 | — | — | — | — | — | — | 20 | 100 | 27.9 | 0 | 26 | 100 | 26.8 | 1 | 29 | 100 | 26.4 | 0 | — | — | — | — |
| 7.5 | — | — | 34 | 92 | 24.6 | 0 | — | — | — | — | — | — | — | — | — | — | — | — | 27 | 96.5 | 27.4 | 0 |
| 8.0 | — | — | — | — | — | — | 20 | 100 | 29.3 | 0 | 25 | 96.5 | 28.3 | 1 | 29 | 100 | 26.4 | 1 | — | — | — | — |
| 8.5 | 145 | 58.6 | 34 | 92 | 26.4 | 0 | — | — | — | — | — | — | — | — | — | — | — | — | 27 | 96.5 | 31.2 | 0 |
| 9.0 | — | — | — | — | — | — | 19 | 95 | 33.3 | 0 | 23 | 92.0 | 32.4 | 3 | 27 | 93 | 30.0 | 0 | — | — | — | — |
| 9.5 | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | 27 | 96.5 | 33.3 | 4 |
| 10.0 | 64 | 25.9 | 33 | 89 | 25.9 | 6 | 18 | 90 | 35.6 | 4 | 21 | 80.5 | 34.2 | 6 | 26 | 89.6 | 31.6 | 6 | — | — | — | — |
| 10.5 | — | — | 31 | 83.6 | 27.3 | 10 | — | — | — | — | — | — | — | — | — | — | — | — | 25 | 89.3 | 35.3 | 9 |
| 11.0 | — | — | — | — | — | — | 16 | 80 | 35.5 | 3 | 18 | 69.2 | 35.8 | 4 | 24 | 82.6 | 33.1 | 10 | — | — | — | — |
| 11.5 | 21 | 8.5 | 29 | 78.4 | 27.0 | 9 | — | — | — | — | — | — | — | — | — | — | — | — | 20 | 71.5 | 36.2 | 13 |
| 12.0 | — | — | — | — | — | — | 15 | 75 | 37.8 | 7 | 15 | 57.5 | 36.9 | 3 | 18 | 62.0 | 34.2 | 10 | — | — | — | — |
| 12.5 | — | — | 23 | 62.3 | 26.3 | 7 | — | — | — | — | — | — | — | — | — | — | — | — | 16 | 51.0 | 35.3 | 12 |
| 13.0 | — | — | — | — | — | — | 14 | 70 | 37.7 | 7 | 13 | 50.0 | 37.0 | 6 | 14 | 48.3 | 34.2 | 6 | — | — | — | — |
| 13.5 | 9 | 3.64 | 20 | 54.0 | 27.8 | 10 | — | — | — | — | — | — | — | — | — | — | — | — | 13 | 46.5 | 36.7 | 9 |
| 14.0 | — | — | — | — | — | — | 12 | 60 | 36.7 | 9 | 13 | 50.0 | 35.7 | 8 | 11 | 37.8 | 35.9 | 3 | — | — | — | — |
| 14.5 | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | 9 | 32.0 | 35.2 | 6 |
| 15.0 | — | — | — | — | — | — | 9 | 45 | 36.2 | 7 | 9 | 34.6 | 36.2 | 5 | 8 | 27.5 | 36.5 | 4 | — | — | — | — |
| 15.5 | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | 5 | 17.8 | 32.6 | 2 |
| 16.0 | — | — | 6* | 22.0 | 27.0 | 2 | 4 | 20 | 30.7 | 2 | 7 | 26.8 | 31.2 | 4 | 7 | 24.1 | 32.2 | 4 | — | — | — | — |

* Data for one cage is missing, hence the % of start is calculated on the basis of the original number in three cages instead of four.

† During the last month the mice were all on a plain pellet diet.

TABLE 4-B. C3H MICE. EFFECT OF ANTIOXIDANTS ON THEIR LIFE SPAN. Adjusted Mortality Data and Weights.

| Age, Months | 2—Mercaptoethylamine Hydrochloride | | | | | | | | 2, 2'-Diaminodiethyl Disulfide Dihydrochloride | | | | | | | | 2—Mercaptoethanol | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 0.5% | | | | 1.0% | | | | 0.5% | | | | 1.0% | | | | 0.5% | | | |
| | No. Living | % of Start | Aver. Wt. | No. with Tumors | No. Living | % of Start | Aver. Wt. | No. with Tumors | No. Living | % of Start | Aver. Wt. | No. with Tumors | No. Living | % of Start | Aver. Wt. | No. with Tumors | No. Living | % of Start | Aver. Wt. | No. with Tumors |
| 1.0 | 28 | 100 | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — |
| 1.5 | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — |
| 2.0 | 28 | 100 | 17.6 | 0 | 25 | 100 | 18.5 | 0 | 27 | 100 | 17.8 | 0 | 28 | 100 | 18.5 | 0 | — | — | — | — |
| 2.5 | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — |
| 3.0 | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — |
| 3.5 | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — |
| 4.0 | 28 | 100 | 23.8 | 0 | 25 | 100 | 25.6 | 0 | 27 | 100 | 24.0 | 0 | 28 | 100 | 23.4 | 0 | — | — | — | — |
| 4.5 | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | 22 | 100 | 23.2 | 0 |
| 5.0 | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — |
| 5.5 | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — |
| 6.0 | 28 | 100 | 24.8 | 0 | 25 | 100 | 26.6 | 0 | 27 | 100 | 26.5 | 0 | 27 | 96.2 | 26.8 | 1 | — | — | — | — |
| 6.5 | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | 22 | 100 | 25.5 | 0 |
| 7.0 | 28 | 100 | 26.5 | 1 | 25 | 100 | 26.8 | 1 | 27 | 100 | 26.9 | 0 | 26 | 93.0 | 25.3(?) | 1 | — | — | — | — |
| 7.5 | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | 22 | 100 | 24.8 | 0 |
| 8.0 | 28 | 100 | 28.4 | 3 | 25 | 100 | 29.4 | 2 | 27 | 100 | 28.4 | 2 | 25 | 89.2 | 27.4 | 0 | — | — | — | — |
| 8.5 | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | 22 | .00 | 24.6 | 0 |
| 9.0 | 26 | 92.8 | 29.5 | 1 | 23 | 92 | 30.9 | 1 | 26 | 96.2 | 30.3 | 6 | 25 | 89.2 | 30.6 | 1 | — | — | — | — |
| 9.5 | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | 22 | 100 | 26.0 | 2 |
| 10.0 | 26 | 92.8 | 30.2 | 4 | 23 | 92 | 32.3 | 2 | 24 | 92.2 | 31.5 | 7 | 25 | 89.2 | 31.0 | 4 | — | — | — | — |
| 10.5 | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | 21 | 95.5 | 26.3 | 4 |
| 11.0 | 26 | 92.8 | 30.6 | 8 | 22 | 88 | 32.5 | 3 | 23 | 85.2 | 32.2 | 8 | 22 | 78.6 | 32.0 | 6 | — | — | — | — |
| 11.5 | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | 19 | 86.5 | 26.0 | 6 |
| 12.0 | 24 | 86.0 | 31.5 | 13 | 20 | 80 | 33.5 | 3 | 20 | 74.0 | 33.7 | 7 | 20 | 71.5 | 34.0 | 7 | — | — | — | — |
| 12.5 | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | 18 | 82.0 | 27.7 | 6 |
| 13.0 | 16 | 57.2 | 32.7 | 4 | 20 | 80 | 32.4 | 9 | 17 | 63.0 | 34.6 | 8 | 17 | 60.6 | 36.7 | 8 | — | — | — | — |
| 13.5 | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | 16 | 72.7 | 32.1 | 8 |
| 14.0 | 12 | 42.8 | 32.6 | 6 | 15 | 60 | 33.2 | 7 | 14 | 51.8 | 33.1 | 5 | 15 | 53.4 | 34.1 | 7 | — | — | — | — |
| 14.5 | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | 14 | 63.5 | 29.5 | 8 |
| 15.0 | 9 | 31.2 | 33.4 | 4 | 9 | 36 | 36.2 | 5 | 11 | 40.5 | 31.2 | 6 | 11 | 39.3 | 31.6 | 8 | — | — | — | — |
| 15.5 | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | 10 | 45.5 | 30.9 | 8 |

TABLE 5. EFFECT OF ANTIOXIDANTS ON THE HALF-SURVIVAL TIME OF AKR AND C3H MICE.

| Group | Age at Which 50% Are Dead | |
|---|---|---|
| | AKR | C3H |
| 1. Controls | | |
| Bar Harbor | 7.5 months ± 1.4* | 9.0 months ± 0.9 |
| Pellets | 7.8 months ± 1.9 | 14.0 months ± 3.2 |
| Powder | 7.5 months ± 2.1 | 14.5 months ± 4.6 |
| 2. Cysteine Hydrochloride | | |
| 0.5% | 9.0 months ± 2.4 | 13.0 months ± 3.6 |
| 1.0% | 10.5 months ± 2.9 | 13.0 months ± 3.4 |
| 3. Ascorbic Acid, 2.0% | 7.5 months ± 2.0 | 12.5 months ± 3.3 |
| 4. 2—Mercaptoethylamine Hydrochloride | | |
| 0.5% | 8.2 months ± 2.2 | 13.5 months ± 3.6 |
| 1.0% | 10.5 months ± 3.1 | 14.5 months ± 4.0 |
| 5. 2, 2'—Diaminodiethyl Disulfide Dihydrochloride | | |
| 0.5% | 10.6 months ± 2.8 | 14.0 months ± 3.8 |
| 1.0% | 7.8 months ± 2.2 | 14.5 months ± 3.9 |
| 6. 2—Mercaptoethanol, 0.5% | 7.6 months ± 2.0 | 15.0 months ± 4.5 |

* Estimate of standard error.

(tail). Lymphatic leukemia was noted in only one, and in this case the animal was almost dead. Also, each month the number of tumors in the living C3H mice were noted.

## RESULTS AND DISCUSSION

Complete mortality data are presented in tables 1 and 2. Tables 3 and 4 present the average weights of the mice, the number living (corrected for losses due to causes other than death by subtracting the number so lost from the number living in each of the months preceding the loss—as can be seen by comparing tables 1 and 2 with tables 3 and 4 these corrections are generally small) and the percentage of the original group (corrected for losses) still living as a function of time in months. The half-survival times (i.e., age at which 50 per cent of the mice were dead) along with an estimate of the standard error for each group of AKR and C3H mice are presented in table 5. The experiment was terminated after 15-16 months. The predicted effect of the reducing agents on the life span of the AKR mice (very few of which were still living) was evident at the end of this period, while no significant trend was noted in the C3H mice.

A 20 per cent increase in the half-survival time of AKR mice was achieved by adding either cysteine (1.0%), 2-mercaptoethylamine (1.0%), or 2,2′-diaminodiethyl disulfide (0.5%) to their diet. The half-survival time of the controls was about 8 months, whereas that of the animals treated as above was about 10 months. At the age of 10 months this result was significant at a P value of 0.01 or less. The influence of these compounds is not through an effect on the lymphatic leukemia which the AKR's developed, as shown by the fact that blood smears taken at 12 and 13 months were all normal except one, and in this case the animal was moribund. These preliminary results are quite encouraging. The effect could easily have been missed as there was no way of determining beforehand just how much of the compounds should be added to the diet of any given strain to yield the desired result.

Ascorbic acid (2.0%) seemed to have no effect on the life span of either the AKR or C3H mice. Likewise, 2-mercaptoethanol (0.5%) had no significant effect on the two strains. This compound is somewhat toxic even at 0.5% as judged by the poor weight gain compared to the other groups.

The serum and tissue levels of the radiation protection compounds depend on the rates of ingestion and excretion and the rate they are metabolized. Of these variables the rate of ingestion is the only one that can be readily controlled. With the powdered diet used in this experiment the animals tended to eat most of their food shortly after it was placed in their cages. This would give a high temporary rise in the level of the compounds with but a relatively low one later on. Hence it would seem desirable to feed the mice more frequently. An experiment has been started in which this, in effect, will be done by feeding the mice pellets to which the chemicals have been added.

## SUMMARY

AKR mice on cysteine hydrochloride (1.0%), 2-mercaptoethylamine hydrochloride (1.0%), or 2,2′-diaminodiethyl disulfide dihydrochloride (0.5%) had a half-survival time (10 months) approximately 20 per cent greater than the controls (8 months). These results are in conformity with the theory that aging may, in part, be due to the deleterious side effects of free radicals normally produced in metabolism. Ascorbic acid (2.0%) and 2-mercaptoethanol (0.5%) did not have a significant effect. No certain effect of any of the 5 compounds used was observed in the C3H mice.

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# EFFECTS OF AGE AND ENDOCRINES ON THE MAST CELL COUNTS OF THE RAT MYOCARDIUM

P. CONSTANTINIDES, M.D., Ph.D., AND J. RUTHERDALE, M.D.
*(From the Anatomy Department, University of British Columbia, Vancouver, B.C., Canada)*

The possible endocrine role of mast cells and their intimate association with systemic connective tissue pose the question of whether these cells are under the functional or mitogenic control of any of the recognized endocrine glands.

While little is known about any such functional relationship at the present time, several investigators recently studied the effects of endocrines, notably glucocorticoids, on the mast cell population of various mammalian tissues (1, 2, 4, 6, 10-14). The conflicting results of these studies are possibly due, at least in part, to the variety of tissues, species, and histologic techniques employed, and to the fact that few of these investigators (4, 6, 11) presented statistically analyzed data.

The present paper reports on the relationships of aging, stress, and the principal endocrine glands to the mast cell population of the rat myocardium studied under standard sampling, fixing, staining, and counting conditions.

## MATERIALS AND METHODS

### A. *Animals and treatments.*

Male Wistar albino rats were used in all except the "female gonad" and the "aging" series of experiments, in which females and animals of both sexes were used, respectively. Each control and experimental group consisted of 7-9 animals. All injections were subcutaneous. The particulars of each treatment, together with the body weight ranges, which varied from experiment to experiment were as follows: 1) *Aging.* Three lots of animals of known birth dates were examined, each consisting of a male and female group; 1 month old (40-60 Gm.), 18 months old (300-400 Gm.), and 24 months old (350-450 Gm.). 2) *Adrenocortical steroids.* Four cortisone experiments were performed: 6 mg./rat/day for 3 weeks, 3 mg./rat/day for 1 week. 0.2 mg./rat/day for 3 weeks, and 0.2 mg./rat/day for 1 week. The initial body weight ranges in these experiments were 200-250 Gm., 300-350 Gm., 200-250 Gm., and 150-200 Gm., respectively. Desoxycorticosterone acetate (DCA) and Upjohn's Lipoadrenal Extract were given to animals weighing 200-250 Gm. for 3 weeks at 3 mg./rat/day and 10 units/rat/day, respectively. 3) *Adrenalectomy and ACTH.* Adrenalectomy was performed in rats weighing 100-150 Gm. (Adrenalectomy I) and 350-400 Gm. (Adrenalectomy II). In both experiments the animals were given glucose and NaCl supplemented water and they were killed 3 weeks after the operation. ACTH (Ciba) was given to 100-150 Gm. rats for 10 days, at 6 mg./rat/day, divided in 3 doses of 2 mg. 4) *Stress.* Rats weighing 200-250 Gm. were subjected to 3 different "stressor" treatments: cold exposure, fasting, and fracture of both hind legs (under ether anesthesia). Cold exposure was applied for 24 hours at 2-5 C., 48 hours at 0-1 C., and 1 week at 1-2 C. Fasting (with free access to tap water) was applied for 24 and 48 hours. The animals of the fracture experiment were killed 24 hours after the operation. 5) *Thyroid.* Thyroidectomy was performed in 120-200 Gm. rats, the animals being killed 3 weeks later. Thyroxine from tablets (Thyroxine I) and Crystalline Thyroxine Sodium (Thyroxine II) were both given for 1 week at 0.2 mg./rat/day to animals weighing 180-220 Gm. and 100-150 Gm., respectively. 6) *Gonads.* All gonadal experiments were performed with 180-230 Gm. rats, except the estradiol experiment in which animals weighing 100-150 Gm. were used. Sacrifice followed 2 weeks after ovariectomy and orchidectomy. Hormone injections were also given for 2 weeks, at the following dosage levels: estradiol benzoate 0.2 mg./rat/day, stilbestrol 1 mg./rat/day, progesterone 2 mg./rat/day, testosterone 2 mg./rat/day. 7) *Hypophysectomy and Pituitary Growth Hormone (Connaught).* The hypophysectomized animals weighed 140-160 Gm. at the time of operation and were killed 3 weeks later. Growth hormone was given to 240-260 Gm. rats for 3

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weeks, at 4 mg./rat/day, divided in 2 doses of 2 mg. 8) *Heparin, Histamine, and Protamine.* These substances were given for 3 weeks to 120-170 Gm. rats at 2 mg./rat/day, 10 μg/rat/day, and 10 mg./rat/day, respectively.

*B. Tissue sampling, histologic and counting technique.*

Mast cells were counted on 10μ thick paraffin sections made from tissues fixed in alcoholic formalin (10 parts of concentrated formalin to 90 parts of 95 per cent ethyl alcohol) and stained with 1 per cent aqueous toluidine blue. The standard myocardium samples were 2 mm. thick slices cut through both ventricles at the maximal diameter of the heart, i.e., close to its base.

Using an etched square frame inserted in the ocular (10X) of the microscope and a low power (10X) objective, all mast cells contained within 10 such frames—covering an actual area of 7 mm.²—were counted in each section. Six adjacent sections were thus counted in each heart, their numerical mean representing the average count figure for the myocardium of each individual animal. The mean mast cell count ± ***E*** (standard error) of every group was computed from 7-9 such figures.

In order to randomize the count areas and to standardize the whole procedure, the 10 frames scanned in each section were divided in two series of 5 frames each, one applied to the anterior, the other to the posterior wall of the left ventricle. The frames of each series were contiguous and successive, forming a strip whose one edge was tangent to the epicardial surface of the myocardium.

A transparent paper tracing of the outline of each section was made, cut out with scissors, and weighed in a microanalytic balance. The weight of each tracing in milligrams constituted an indirect measure of the total area of each section. Since all sections were taken from a slice of standard location, these tracing weights were also approximate indices of the heart size with sufficient comparative value. The mean section tracing weight ± ***E*** of each group was computed from individual numerical means as above.

*C. Assessment of specific effectiveness of the treatments.*

To evaluate the specific effectiveness of the various hormone injections and endocrine operations, suitable morphologic endpoints of hormone action or withdrawal were studied in most experiments. Since in most instances the amounts of hormones injected were far above the threshold level, their morphologic effects on suitable target organs were clearly evident by gross inspection or microscopic examination and, therefore, not tabulated.

The criteria used for morphologic evaluation of the endocrine treatments were as follows: 1) *Adrenal:* compensatory adrenal atrophy (for injected adrenal steroids) and adrenal enlargement (for stress and ACTH). 2) *Gonads:* uterine estrus (macroscopic) and vaginal estrus (microscopic) for estrogens; uterine atrophy for ovariectomy, progestational endometrial reaction (microscopic) for progesterone; seminal vesicle hypertrophy for testosterone; and seminal vesicle atrophy for orchidectomy. 3) *Thyoid:* atrophy of follicular epithelium and increase of follicular colloid (microscopic) for thyroxine injections. 4) *Hypophysectomy:* growth arrest and testicular, seminal vesicle, and adrenal atrophy. 5) *Pituitary Growth Hormone:* acceleration of growth.

In addition, the completeness of all operations was verified at autopsy.

With the exception of thyroidectomy, adrenalectomy, protamine, heparin, and histamine (for which no specific indices of action were studied), satisfactory evidence of specific effectiveness was obtained for all treatments included in this paper.

## RESULTS

A preliminary report on some results of this study has been presented previously (5). The present paper contains the data of most of the original and many new experiments. With the exception of the findings that adrenalectomy increases and thyroxine decreases the mast cell counts (which were of borderline significance), all the originally reported effects could be repeated.

1) *Age and sex (table 1).* Aging was associated with a significant drop of the myocardial mast cell count in both sexes between the first and the eighteenth month, and in males between the eighteenth and the twenty-fourth month of age. The differences between the counts of the 18 and 24-month-old males seem to reflect a true diminution of the myocardial mast cell population, since there was no significant difference between the mean heart size of

## Tables of Results

### Table 1. Age and Sex.

| Group | Mean Number of Mast Cells per 7 mm.² Myocardium ± E | Mean Area of Heart Section (mg. wt. of Tracing) ± E |
|---|---|---|
| ♂ 1 month old | 44.2 ± 3.6 | 0.9 ± 0.26 |
| ♀ 1 month old | 35.7 ± 2.6 | 0.6 ± 0.04 |
| ♂ 18 month old | 20.2 ± 1.9 | 2.7 ± 0.13 |
| ♀ 18 month old | 17.4 ± 2.6 | 2.1 ± 0.18 |
| ♂ 24 month old | 12.2 ± 0.5 | 2.6 ± 0.30 |
| ♀ 24 month old | 12.3 ± 1.1 | 2.7 ± 0.24 |

### Table 2. Adrenal Steroids.

| | | |
|---|---|---|
| controls | 28.6 ± 2.1 | 2.2 ± 0.18 |
| DCA, 3 mg./rat/day, 3 weeks | 30.5 ± 2.0 | 2.1 ± 0.13 |
| lipoadrenal extract, 10 units/rat/day, 3 weeks | 31.1 ± 2.6 | 2.2 ± 0.19 |
| cortisone, 6 mg./rat/day, 3 weeks | 13.2 ± 2.3 | 2.0 ± 0.19 |
| controls | 10.8 ± 0.5 | 2.6 ± 0.13 |
| cortisone, 3 mg./rat/day, 1 week | 4.8 ± 0.6 | 2.4 ± 0.18 |
| controls | 37.8 ± 1.5 | 1.8 ± 0.08 |
| cortisone, 0.2 mg./rat/day, 1 week | 17.1 ± 1.1 | 1.6 ± 0.16 |
| controls | 28.1 ± 2.8 | 2.1 ± 0.05 |
| cortisone, 0.2 mg./rat/day, 3 weeks | 25.8 ± 2.0 | 2.0 ± 0.19 |

### Table 3. Adrenalectomy and ACTH.

| | | |
|---|---|---|
| controls | 23.3 ± 1.3 | 1.7 ± 0.17 |
| adrenalectomy I | 25.2 ± 2.0 | 1.3 ± 0.16 |
| controls | 12.0 ± 1.2 | 2.8 ± 0.07 |
| adrenalectomy II | 8.0 + 1.1 | 2.7 ± 0.11 |
| controls | 38.5 ± 0.9 | 1.6 ± 0.13 |
| ACTH, 6 mg./rat/day, 1 week | 36.2 ± 2.0 | 1.7 ± 0.12 |

### Table 4. Stress.

| | | |
|---|---|---|
| controls | 21.5 ± 4.2 | 2.2 ± 0.13 |
| cold, 24 hours | 21.4 ± 1.9 | 2.2 ± 0.09 |
| controls | 19.5 ± 1.1 | 2.1 ± 0.06 |
| cold, 48 hours | 17.2 ± 1.2 | 1.7 ± 0.13 |
| controls | 23.4 ± 1.7 | 2.0 ± 0.09 |
| cold, 1 week | 28.6 ± 1.3 | 1.9 ± 0.18 |
| controls | 20.0 ± 1.0 | 2.4 ± 0.13 |
| fasting, 24 hours | 29.0 ± 4.5 | 2.4 ± 0.12 |
| fasting, 48 hours | 26.0 ± 1.5 | 2.2 ± 0.62 |
| controls | 20.0 ± 3.3 | 2.0 ± 0.17 |
| fracture | 29.0 ± 1.7 | 2.0 ± 0.12 |

### Table 5. Thyroid.

| Group | Mean Number of Mast Cells per 7 mm.² Myocardium ± E | Mean Area of Heart Section (mg. wt. of Tracing) ± E |
|---|---|---|
| controls | 29.0 ± 1.1 | 1.8 ± 0.02 |
| thyroidectomy | 22.8 ± 5.4 | 1.5 ± 0.13 |
| controls | 25.3 ± 3.1 | 2.2 ± 0.19 |
| thyroxine I, 0.2 mg./rat/day, 1 week | 21.5 ± 3.0 | 2.4 ± 0.12 |
| controls | 59.2 ± 9.4 | 1.6 ± 0.29 |
| thyroxine II, 0.2 mg./rat/day, 1 week | 52.2 ± 4.6 | 1.5 ± 0.15 |

### Table 6. Female Gonad.

| | | |
|---|---|---|
| controls | 45.1 ± 2.9 | 1.8 ± 0.06 |
| ovariectomy | 43.7 ± 3.9 | 2.0 ± 0.04 |
| estradiol, 0.2 mg./rat/day/, 2 weeks | 33.5 ± 2.3 | 1.8 ± 0.12 |
| ovariectomy | 23.8 ± 0.8 | 2.3 ± 0.32 |
| ovariectomy + stilbestrol, 1 mg./rat/day, 2 weeks | 14.6 ± 1.0 | ..... |
| ovariectomy + progesterone, 1 mg./rat/day, 2 weeks | 23.4 ± 3.9 | ..... |

### Table 7. Male Gonad.

| | | |
|---|---|---|
| controls | 27.1 ± 2.1 | 2.2 ± 0.19 |
| orchidectomy | 32.2 ± 3.1 | 2.3 ± 0.23 |
| orchidectomy + testosterone, 2 mg./rat/day, 3 weeks | 28.5 ± 5.3 | 2.1 ± 0.05 |

### Table 8. Pituitary.

| | | |
|---|---|---|
| controls | 20.8 ± 2.7 | 2.4 ± 0.22 |
| hypophysectomy | 33.2 ± 2.6 | 1.5 ± 0.15 |
| controls | 30.4 ± 4.9 | 2.4 ± 0.07 |
| pituitary growth hormone, 4 mg./rat/day, 3 weeks | 20.4 ± 1.3 | 2.7 ± 0.14 |

### Table 9. Protamine, Heparin, Histamine.

| | | |
|---|---|---|
| controls | 43.3 ± 3.7 | 1.8 ± 0.18 |
| protamine, 10 mg./rat/day, 3 weeks | 37.0 ± 2.3 | 1.7 ± 0.12 |
| heparin, 2 mg./rat/day, 3 weeks | 33.0 ± 2.9 | 1.6 ± 0.09 |
| histamine, 10 μg/rat/day, 3 weeks | 48.9 ± 3.1 | 1.8 ± 0.15 |

the two groups. On the other hand, the differences between the counts of weanlings and 18-month-old animals of both sexes seem to be relative, since the diminution of mast cell counts was paralleled by a significant enlargement of the heart size in these groups. In other words, it seems that the absolute number of mast cells did not decrease in the latter cases, but that these cells merely failed to proliferate in step with the growing heart mass. No significant sex difference appeared in any age group examined. 2) *Adrenal steroids (table 2).* Of the injected corticoids, DCA and lipoadrenal extract had no effect (at the dosages and treatment durations used) but cortisone significantly depressed the counts when given at a high dosage level for one or three weeks and at a low dosage level for one week. Since no significant change of the heart size was evident under those conditions, the cortisone-induced depression of mast cell counts seems to reflect a true diminution of the absolute number of stainable mast cells in the myocardium. It is, however, noteworthy that the depressing effect of low dosage cortisone disappeared when the treatment was prolonged to 3 weeks. 3) *Adrenalectomy and ACTH (table 3).* Neither adrenalectomy nor ACTH had any effect. 4) *Stress (table 4).* All three types of stress studied (cold exposure, fasting, and fracture) failed to affect the mast cell counts at the durations tested. The moderate increases in the counts of several stressed groups are of only borderline significance. 5) *Thyroid (table 5).* Both types of thyroxine and surgical thyroidectomy failed to influence the mast cell counts. 6) *Female gonad (table 6).* Ovariectomy and progesterone had no effect, but injected estrogen (both natural and synthetic) significantly depressed the mast cell counts. Since estradiol did not influence the heart size, it seemed to diminish the absolute myocardial mast cell population. 7) *Male gonad (table 7).* Neither orchidectomy nor injected testosterone had any effects on the counts. 8) *Hypophysectomy and pituitary growth hormone (table 8).* Hypophysectomy significantly increased, whereas growth hormone exerted a depressor effect of borderline significance on the counts. Since hypophysectomy caused a significant shrinkage of the heart size whereas growth hormone exhibited a trend towards enlargement of that organ, the two effects are most probably relative, i.e., the absolute number of myocardial mast cells most likely remained unaffected. 9) *Protamine, heparin, histamine (table 9).* None of these three agents had any significant effect on the mast cell counts.

## DISCUSSION

Although the absolute population of myocardial mast cells was not directly counted in this study, the present findings indicated that the number of these cells did not increase to parallel the growth of the heart mass from the second to the twenty-fourth month of the life span or the growth induced by injections of pituitary somatotrophin. Indeed, their counts per unit myocardial area progressively declined with increasing age, within the time interval studied.

It is of interest that Hellström and Holmgren (7) found significantly lower mast cell counts in the myocardium of old individuals as against young adults, and that Cairns and Constantinides (3) reported a significant drop in the myocardial counts of old female atherosclerotic individuals but only a trend toward a drop in old female non-atherosclerotic individuals, as compared to young non-atherosclerotic adults.

The report of Padawer and Gordon (8) that the number of mast cells in the peritoneal fluid of the rat increases with increasing body weight is not necessarily in conflict with the myocardial findings of the present study. Any attempt at a correlation between those two sets of data will have to await the clarification of the relationships between the mast cells of the various body fluids and those of the connective tissue in various regions of the body.

It should be further underlined that our findings apply only to a portion of the extrauterine life span. We have no data on the myocardium of fetuses or newly born rats. Since there is evidence that mast cells appear late in fetal life or soon after birth in several species (9), and that the myocardium of newly born humans exhibits remarkably lower counts than that of young adults,* it is possible that the age-associated decline of the myocardial mast cell counts in the rat is preceded by a period of rapid increment during late fetal life or weaning.

None of the endocrines studied was found to stimulate proliferation of the myocardial mast cells. On the contrary, evidence was ob-

* Unpublished observation by the authors.

tained that injected high doses of cortisone will diminish the apparent myocardial mast cell concentration, whether given for a short or a long period of time. On the other hand, low doses of cortisone displayed a similar effect only when administered for a short period.

Our findings with cortisone are in general agreement with the statistical data of Cavallero and Braccini (4) on mast cells of the rat myocardium and with the statistical data of Smith and Atkinson (11) on mast cells of the mouse uterus. They are also in line with the qualitative reports of Asboe-Hansen (1), Bloom (2) and Stuart (13). It is interesting that Smith and Atkinson (11) observed a phenomenon of mast cell "resistance" developing to prolonged administration of high dosage cortison, similar to that observed in our own experiments following prolonged treatment with low dosage cortisone.

Directly opposed to our own results and those of the above authors are the statistical data of Devitt and associates (6) on the mast cells of the rat myocardium, skeletal muscle, and mesentery. Also divergent are the counts (unaccompanied by standard errors) of Schoch and Glick (10) in rat skin and of Smith and Lewis (12) in hamster skin, mesentery, and cheek pouch, as well as the qualitative reports of Zachariae and Moltke (14) on the effect of hydrocortisone on rabbit skin mast cells. All these authors failed to observe any effects of glucocorticoids on mast cell numbers. It is noteworthy, however, that the latter two teams reported a great increment in the percentage of abnormal (i.e., degranulated and vacuolated) mast cells after injection of cortisone and hydrocortisone, respectively. Should degranulation and vacuolation precede the disappearance of mast cells, it might be expected that some authors would find merely an increase in the percentage of abnormal forms and others a diminution of the total count, depending on the degree of the effect and on conditioning factors. It should also be kept in mind that with the exception of the studies of Devitt and associates (6) the other three (10, 12, 14) were made in organs other than the heart, and the last two (12, 14) in species other than the rat. It is possible that the sensitivity of mast cell counts to cortisone varies with the species and the tissue examined as well as with the amount injected and the duration of treatment.

At any rate, it was found that changes in the level of endogenous cortical steroids, as induced by adrenalectomy, ACTH injections, and three different types of stress exposure (acute or chronic), did not influence the mast cell counts. Similar results were reported by Smith and Lewis (12) regarding the effects of adrenalectomy and ACTH on the mast cell counts of the mesentery, the skin, and the cheek pouch of the hamster, and by Schoch and Glick (10) concerning the effects of ACTH and chilling on the mast cell counts of rat skin. It must, therefore, be concluded that the actions of injected cortisone are pharmacologic.

On a similar basis, since ovariectomy and sex difference did not influence the counts, the observed depressor effect of injected estrogen, which was confirmed by the findings of Smith and Atkinson (11), cannot be considered physiologic.

Since we also found that neither thyroidectomy nor injected thyroxine affect the counts, the latter in agreement with the report of Devitt and associates (6), we must conclude that the mast cell population of the rat myocardium is not controlled by the physiologic activity of the adrenal cortex, the gonads, or the thyroid. This evidently does not exclude any possible functional relationships with these glands which might exist without affecting the number of visible mast cells in the rat heart.

The mechanism of the effects of injected cortisone and estrogen is obscure. Since these principles might act by causing degranulation or loss of tinctorial affinity of mast cell granules for toluidine blue, thereby diminishing the number of visible mast cells, chemical studies of heparin and histamine levels in tissues and tissue fluids of injected animals might help in clarifying this problem.

Finally, these results should not be taken as indicative of the response of mast cell populations in all organs or all species. It is possible that mast cells of different organs respond differently to the same hormonal stimuli. Furthermore, the finding that in humans, unlike rats, there is a sex difference (7, 3), suggests that different mast cell-endocrine relationships may prevail in different species.

## SUMMARY

The influence of age, endocrines, and certain drugs on the mast cell counts (m.c.c.) per unit area of the rat myocardium was studied. It was found that:

Aging was associated with a significant diminution of the m.c.c. in both sexes.

Adrenalectomy, ACTH injections, and acute or chronic stress (cold, fasting, and fracture) failed to affect the m.c.c. Of the injected adrenocortical steroids, DCA and lipoadrenal extract had no effect, but cortisone produced a significant depression of the m.c.c. when given at a high dosage level for one or three weeks and at a low dosage level for one week.

Thyroidectomy and injected thyroxine had no effect on the m.c.c.

Ovariectomy and injected progesterone failed to affect the m.c.c., but injected estrogen significantly depressed them. No sex difference was observed among animals belonging to the same age group.

Orchidectomy and injected testosterone had no effect on the m.c.c.

Hypophysectomy significantly increased the m.c.c.

Protamine, heparin, and histamine had no significant effects on the m.c.c.

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# SKELETAL LESIONS PRODUCED BY CHRONIC TREATMENT WITH SOMATOTROPHIC HORMONE (STH) AND AMINOACETONITRILE (AAN)

HANS SELYE, M.D., Ph.D., D.Sc.

*(From the Institut de Médecine et de Chirurgie expérimentales, Université de Montréal, Montreal, Canada)*

It has been the principal aim of our laboratory to demonstrate the participation of hormones in the pathogenesis of various non-endocrine diseases, that is, of maladies which are not the immediate consequence of primary derangements in the function of endocrine glands. Up to quite recently such hormonal participation had been most clearly proved for diseases in which inflammation and hyaline degeneration of mesodermal structures play a prominent part (e.g., the rheumatic diseases, periarteritis nodosa, malignant nephrosclerosis). During the past year it became evident, however, that hormones can also exert a decisive influence upon the development of bone lathyrism. This malady develops most readily in young animals fed on diets rich in seeds of *lathyrus odoratus* or on certain other closely related plant species. It can also be elicited by some nitriles; one of these, $\beta$($\gamma$-L-glutamyl)aminopropionitrile, could be isolated from the seeds of *lathyrus odoratus*, but synthetic aminocetonitrile (AAN) is even more effective in this respect. The literature on the participation of hormones in non-endocrine diseases (8) and on lathyrism (15) has been recently reviewed elsewhere so that it need not be discussed at length here. It is particularly pertinent to the topic of this communication, however, that rats fed large amounts of *lathyrus odoratus* seeds develop lesions in the epiphyseal plates, kyphoscoliosis, degeneration and herniation of intervertebral disks, periosteal new-bone formation, skeletal changes resembling Legg-Perthes' disease or Paget's disease, and, in rare instances after many months of treatment, even degenerative arthritis. It has been pointed out that "every one of these disorders observed in rats fed *lathyrus odoratus* seeds has a counterpart in diseases in humans" (2, 3), hence a study of experimental lathyrism may have its clinical implications.

It is interesting that in young animals experimental bone lathyrism can be obtained with much smaller doses of lathyrogenic compounds than those required for its production in old animals. In the young the skeletal derangements are mainly characterized by an intense and irregular proliferation of the growth-cartilage plates (which eventually leads to epiphyseal slipping) and pronounced proliferation of incompletely ossified periosteal bone with numerous hemorrhages. An increase in the dosage of the lathyrogenic compounds merely aggravates these same changes and eventually leads to death, but in the young it does not produce degenerative arthritis or any marked deformity of hard, fully mineralized bone (except at the sites of occasional spontaneous fractures). Only very prolonged treatment can produce a typical picture of chronic degenerative and deforming skeletal disease, and in a short-lived laboratory animal such as the rat it is impossible to apply a sufficiently long-lasting treatment during the brief period of youth. It is of special interest, therefore, that treatment with the growth hormone, or somatotrophic hormone (STH) renders even sexually mature rats highly sensitive to small doses of AAN. Indeed, under the influence of combined treatment with STH and AAN, intensely deforming osteoarticular lesions can be obtained, within a few weeks, both in intact (10) and in hypophysectomized (12) adult rats.

In connection with the age factor it is also noteworthy that topical stress in bones plays an extremely important part in the development of skeletal lathyrism. It had long been known that, in lathyritic rats, exostoses are most common at tendon-insertion sites; more recently it has also been noted that under the influence of AAN giant callus formation occurs at fracture sites (9). Furthermore, limbs

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Mr. Kai Nielsen prepared the photographs.

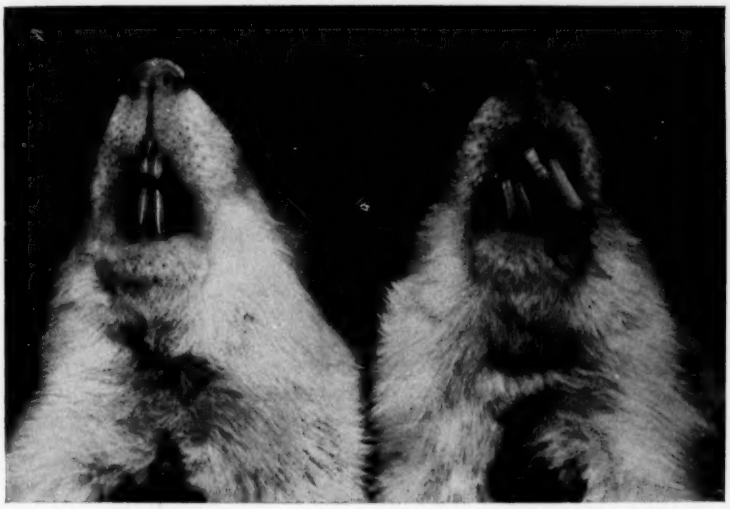

Fig. 1. Incisor teeth of a rat treated with AAN alone (left) and of one which received the same dose of AAN as above and STH. In the former rat the teeth are essentially normal, while in the latter there is marked malocclusion with several cross lines of enamel defects and excessive growth in length. The tips of the upper incisors have turned upwards and are growing into the palate and lips. Experiment I.

inactivated by spinal cord transection are largely protected against the development of skeletal lathyrism. Conversely, excessive compensatory activity of one extremity—e.g., fracture of a bone causing overusage of the contralateral side—increases the bony changes in the overworked part and, except at the fracture site itself, diminishes them everywhere in the limb which is sparingly used, because of the pain induced by the fracture (11).

STH, the growth hormone, is an endocrine secretion which was thought to exert its primary (if not its only) physiologic function during the period of youth, when growth in length is still possible. Yet, in the experiments just mentioned (10), where STH was given conjointly with AAN, the growth hormone did not promote, but actually inhibited, growth in length; nevertheless, it enhanced the development of abnormal bone proliferation. Hence, it would be quite conceivable that an excessive endogenous production of STH might produce deforming skeletal and joint lesions in elderly people without any detectable evidence of gigantism or acromegaly. Incidentally, osteoarthritic changes are particularly common in acromegalics (5).

Earlier experiments with pituitary implants or impure anterior lobe extracts are difficult to interpret. These treatments induce a complex hormonal disturbance with an excess not only of STH but also of other pituitary hormones, such as the gonadotrophins, ACTH, and thyrotrophin. All of these substances are known to cause skeletal changes, and in many respects the effects of these hormones upon bones and joints are mutually antagonistic (4, 13, 14). Prolonged treatment with purified STH preparations can produce an ankylosing polyarthritis, especially in hypophysectomized rats in which the antagonistic effect of ACTH is eliminated (1, 6, 7), but these changes are never as pronounced or as constant as those elicited by combined treatment with STH and AAN. In any event, STH treatment in itself does not produce lesions comparable to senile osteoporosis; on the contrary, it stimulates bone development.

In view of these observations, the question arose whether an excessive endogenous secretion of STH (perhaps in combination with some metabolic factors which, like AAN, are toxic for the skeleton) might participate in the pathogenesis of deforming osteoarticular lesions, such as are common among the old. Of course, in senile people osteoporosis tends to develop concurrently with the deforming osteoarticular changes, while in lathyrism bone formation was

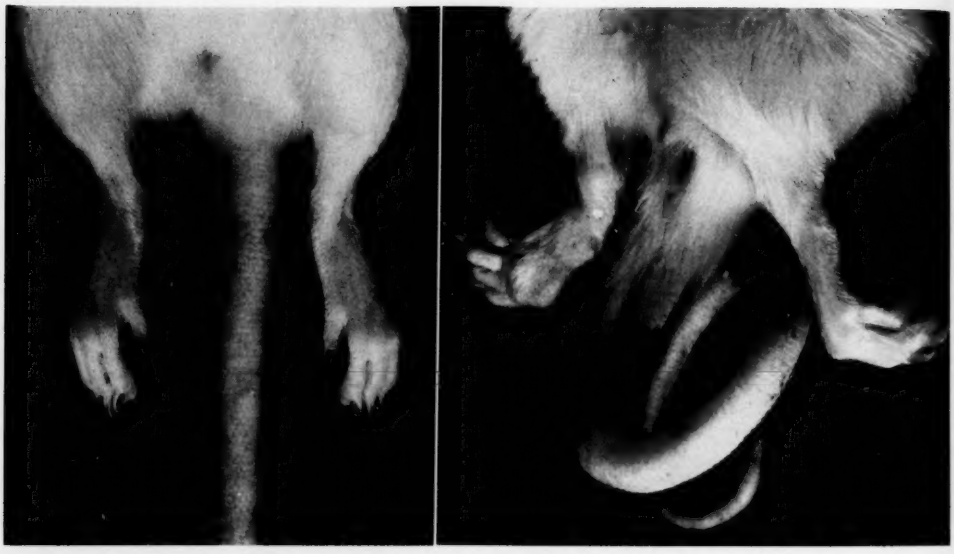

Fig. 2. Essentially normal hind paws and tail of a rat treated with AAN alone (left) in comparison with the intensely deformed arthritic paws and the typically curled tail of a rat which had been given AAN in combination with STH. Experiment I.

always excessive under the experimental conditions used up to date. There still remained the possibility that long-lasting treatment with AAN and STH might more closely duplicate the skeletal changes characteristic of senility, and it is the object of this communication to report upon experiments designed to explore this point.

## MATERIALS AND METHODS

Thirty-five female Sprague-Dawley rats, having an initial body weight of 45-54 Gm., were subdivided into three groups, each having a mean initial body weight of 50 Gm. Group I acted as untreated controls, Group II received AAN and Group III, AAN plus STH.

AAN was administered in the form of aminoacetonitrile hydrosulphate. The daily dose had to be adjusted throughout the experiment. Treatment was stopped whenever the animals in Group III became manifestly ill owing to the sensitizing effect of STH. However, for the sake of uniformity, equal AAN treatment was given to Groups II and III as follows: 10 mg. in 0.2 ml. of water were injected subcutaneously twice daily between the 1st and the 5th day, every 2nd day between the 10th and the 38th day; no injection was given on the 38th and the 39th day and, from then on, injections on alternate days were again given until the 80th day, at which time treatment was stopped.

STH ("Somatotropin," Armour, Lot No. P6108) was administered subcutaneously at the dose of 2 mg. in 0.2 ml. of water twice daily from the 1st until the 80th day without interruption. Unfortunately, the available supply of STH did not permit us to run controls treated with STH alone in the present experiment, but numerous previous acute and chronic experiments with the same lot of STH performed in this and other laboratories have shown that this preparation is not toxic. It is therefore highly probable that the mortality in the rats of Group III was due to the combined effect of AAN plus STH, which resulted in wide-spread skeletal deformities with secondary compression of the central nervous system due to kyphoscoliosis.

Throughout the period of observation all animals had free access to Purina Fox Chow and Mixed Cereal Pablum. No deaths occurred in Groups I and II, but 6 animals died in Group III (1 on the 18th day and 5 between the 38th and 44th day of treatment). Marked skeletal lathyrism was evident in all of the rats that died.

All the surviving animals were killed with chloroform 20 days after the end of treatment,

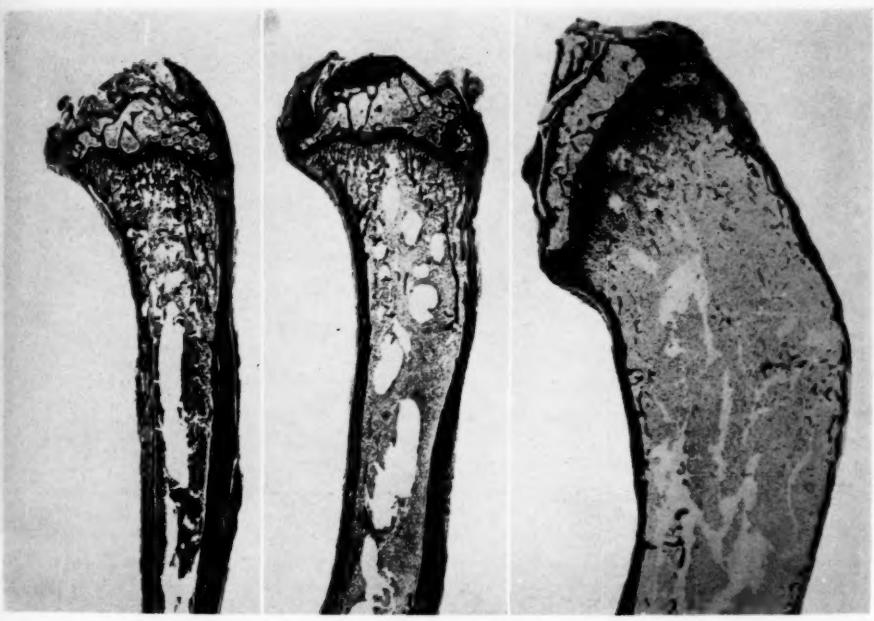

Fig. 3. Low magnification of sagittal longitudinal sections through the upper two-thirds of the tibia of a normal (left), an AAN-treated (middle), and an AAN-plus-STH-treated rat. AAN in itself produced no change visible at this magnification, but in combination with STH caused backward slipping of the epiphysis, great widening of the marrow-cavity, and thinning of the shaft (especially on the anterior surface of the bone). The bone-marrow in the last animal is almost white because of the fatty transformation; dark hemopoietic tissue remains only in the immediate vicinity of the cartilage plate (X 5, aldehyde fuchsin). Experiment I.

that is, on the 100th day after the initiation of the experiment; representative specimens of their skeleton were fixed and simultaneously decalcified in Susa solution. Paraffin-embedded sections were then stained with hematoxylin eosin, Gomori's aldehyde fuchsin stain, and the Hotchkiss-McManus PAS technique.

## RESULTS

Even prior to autopsy, a synergism between STH and AAN became clearly visible by mere examination of the external appearance of the animals. While the rats receiving AAN alone did not differ significantly from the controls, those treated with STH and AAN developed marked skeletal deformities. Towards the end of the first month it was noted that, in these latter rats, the metaphyses of the long tubular bones were greatly enlarged, especially in the region of the growth-cartilage plates. This was particularly obvious in the knee and elbow joints, but palpable exostoses had also developed at muscle-insertion sites on the jaw, occiput, and femur. The tibia became greatly deformed because of backward slipping of the proximal epiphysis. At the same time club-like swellings deformed the distal ends of the tarsal bones and resulted in a lateral deviation of the digits. By the end of the second month these skeletal deformations were extremely pronounced in all the rats of Group III so that the animals could move about only with great difficulty. By this time the thorax also became grotesquely deformed with the xyphoid pointing straight forward, while the spine showed both kyphosis and scoliosis. During these later stages the tails of all animals curled up in a spiral fashion and could not be straightened out even by traction; we later found out that this was due to arthritic changes in the vertebrae. The animals also had great difficulty in chewing their food, because the incisor teeth were no longer functional owing to malocclusion and extreme growth in length. In all the rats in Group III the upper incisors eventually grew in semilunar fashion, protruding backward into

Fig. 4. Region from the tibial shaft of a rat treated with AAN plus STH (left). Here fatty marrow has invaded the shaft. A thin plate of endosteal bone is still preserved, but its upper half is perforated by marrow at several places (X 9, hematoxylin eosin). Under high magnification (right) the basophilic bone globules which are rather characteristic (though not pathognomonic) of lathyrism are clearly visible as dark, round granules within the osseous tissue. The strongly basophilic cement lines give the picture its Paget's disease-like mosaic structure. The vascular channels are greatly dilated (X 480, hematoxylin eosin). Experiment I.

the plate or upward along the lips outside the mouth. On the anterior surface of these incisors there were horizontal defects in the enamel. In order to permit food intake it was repeatedly necessary to clip the teeth with a pair of Linton bone forceps. No such lesions were observed in any of the rats of Groups I and II, but it is noteworthy that similar dental derangements do occur occasionally among untreated senile rats of the Sprague-Dawley strain (figs. 1 and 2).

Histologic examination confirmed that, at the dose level employed in these experiments, AAN alone produced only minor changes in bone structure and virtually no alteration in the appearance of the bone marrow. Conversely, AAN given in combination with STH resulted in considerable derangements in the architecture of both osseous and myeloid tissue. For example, sagittal cross sections through the tibia, viewed at low magnification, revealed an enormous enlargement in the marrow cavity of the rats treated with AAN and STH; at the same time the shaft became extremely thin. The proximal tibial epiphysis was attached on the dorsal surface of the bone, due to slipping of the growth-cartilage plate. The marrow cavity no longer contained active hemopoietic tissues (except occasionally, in the immediate vicinity of the cartilage-plates) but contained only fatty marrow, such as is normally seen in senile rats. This change is all the more noteworthy because our animals were only about 4 months old at the time of autopsy (fig. 3).

The widening of the marrow space is apparently due to the fact that, under the combined influence of AAN and STH, at first there is a marked periosteal bone proliferation which leads to a great thickening of the shaft—as shown by our earlier investigations (10)—but later, endosteal bone absorption leads to an eccentric atrophy of the bone. Often the innermost layers of the originally very thick shaft persist for quite some time after the intermediate layers (between endosteal and periosteal bone) have already been absorbed and replaced by fatty marrow. Then the residual endosteal bone is perforated in many places and gradually disappears (fig. 4, left).

Throughout the skeletal system there developed numerous "basophilic globules" within the bone tissue. These are roundish granules

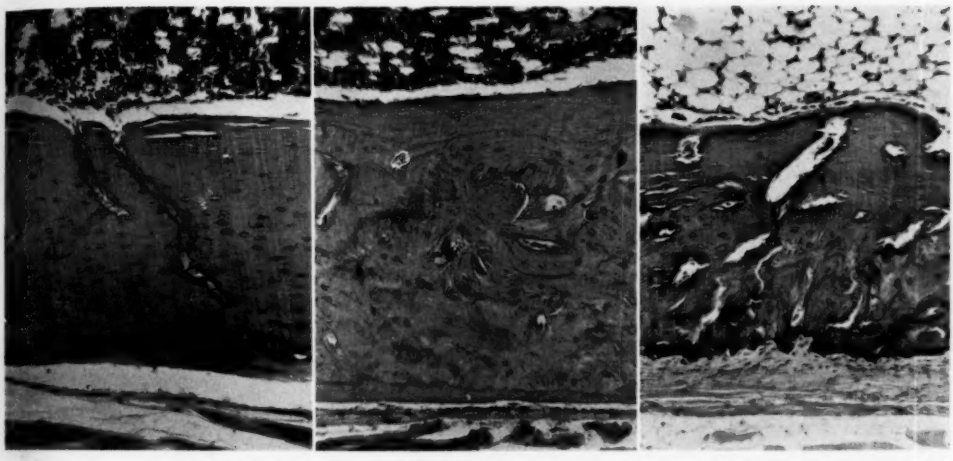

Fig. 5. Sections through periosteum (bottom) bone shaft and bone-marrow of the tibia of a normal (left), AAN-treated (middle) and AAN-plus-STH-treated rat (right). In the normal animal, the shaft is of medium thickness, and all osteocytes are arranged parallel to the longitudinal axis of the bone in line with the lamellae. The vascular channels are narrow, the marrow is purely myeloid. Treatment with AAN caused a moderate thickening of the shaft with some loss in the regular orientation of osteocytes and lamellae. The bone-marrow remains essentially normal. Combined treatment with AAN plus STH led to a thinning of the shaft with considerable dilatation of the vascular channels. The osteocytes and the lamellae are quite irregularly arranged. The bone is eroded by deep lacunae (especially on its periosteal surface), and the marrow is almost completely fatty (X 60, hematoxylin eosin). Experiment I.

varying in diameter from several micra to hardly visible dust-like particles. They stain intensely with hematoxylin and—especially after being mordanted with 1 per cent oxalic or 0.8 per cent periodic acid for five minutes—with Gomori's aldehyde fuchsin technique (9). In the rat, the shafts of long bones consist almost exclusively of circumferential lamallae, which run parallel to the periosteum, while haversian canal systems and cement lines are very poorly developed. Hence it was particularly striking that in all of the rats of Group III an extraordinarily polymorph mottle of lamellar systems had arisen with intensely basophilic cement lines resembling the mosaic pattern of Paget's disease. At the same time, the canals that carry the blood vessels were greatly dilated, as is the case in senile atrophy (fig. 4, right).

AAN alone caused only minor derangements in the architecture of the bone shaft. There was some increase in the thickness of the compact bone and a tendency to irregular arrangement of osteocytes. Conversely, combined treatment with AAN and STH eventually resulted not only in a considerable thinning of the shaft as a whole, but also in a weakening of its structure, due to the porosis caused by the enlargement of the vascular channels (fig. 5).

Pronounced changes were also observed in the junction-cartilage plates. For example, in the proximal growth-cartilage of the tibia AAN alone produced no detectable alteration, but AAN plus STH resulted in a premature cessation of growth in length. The cartilage plates became extremely thin, and the chondrocytes were no longer arranged in regular columns as is usually the case in rats of this age. Furthermore, the primary bone spicules had completely disappeared along the diaphyseal aspect of the junction-cartilage plate, and here a horizontal ossified lamella sealed off the growth-cartilage region (fig. 6). At many places the plate was actually perforated, and either solid bone or canals of bone-marrow were seen between epiphysis and diaphysis.

The changes in the joints (knee, hip, metatarso-phalangeal, etc.) were those characteristic of chronic degenerative arthritis. In many places, the articular surface became eroded, and the cartilage itself underwent fibrillar degeneration. Eventually parts of the joint-cartilage became detached, and freely floating cartilage bodies ("joint mice") were often found in the

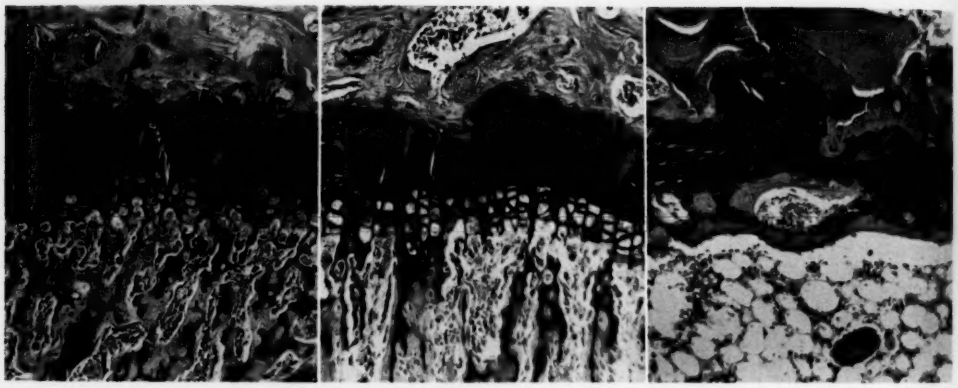

Fig. 6. Growth-cartilage plates of the three tibiae shown in Fig. 5. AAN alone caused no obvious change compared with the normal; AAN plus STH led to a considerable thinning of the cartilage plate; the columnar arrangement of chondrocytes is lost, and primary bone spicule formation no longer occurs on the diaphyseal surface, which is sealed off by solid bone from the fatty marrow (X 60, hematoxylin eosin). Experiment I.

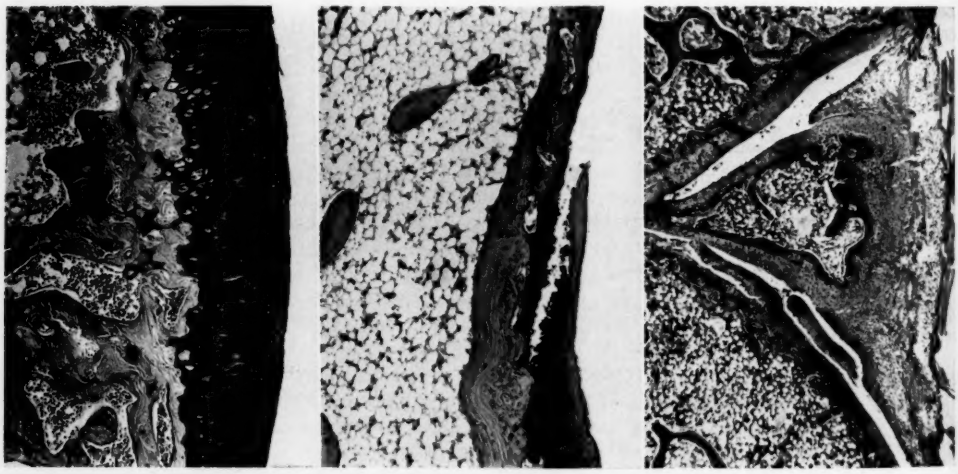

Fig. 7. Left: distal joint-surface of the femur of a rat treated with AAN alone. The cartilage is normal (X 40, aldehyde fuchsin). Middle: corresponding region in a rat treated with AAN and STH. Here the cartilage is intensely stained and partly transformed into a granular material which begins to detach itself. In the upper part of the field the bone is in direct contact with the joint-cavity (X 40, aldehyde fuchsin). Right: part of the knee-joint of a rat treated with STH and AAN. The meniscus is essentially normal, but underneath it the tibial joint-cartilage is largely detached, and part of it has been transformed into a free "joint mouse" (X 18, hematoxylin eosin). Experiment I.

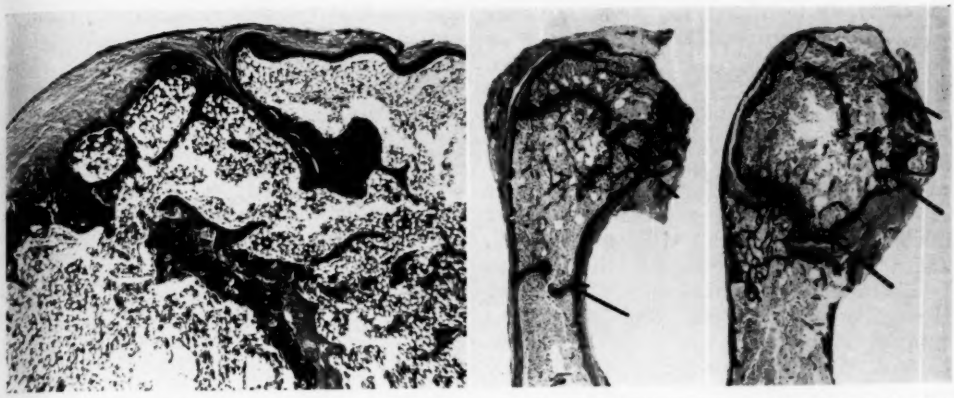

Fig. 8. Three sections from femora of rats which received combined treatment with AAN and STH (second experiment). Left: distal femoral joint-surface with pannus formation and loss of cartilage on the joint-surface. The growth-cartilage plate is thin and perforated at one point (X 16, hematoxylin eosin). The other two femora illustrate the splitting of the growth-cartilage into two (middle) or three (right) plates indicated by arrows. Most of the plates are perforated by marrow channels (X 2¾, hematoxylin eosin). Experiment II.

synovial fluid. Sometimes large areas of the joint-surface became completely denuded of cartilaginous covering (fig. 7).

After completion of this work, the entire experiment was repeated on three groups of 20 rats each, under essentially identical conditions except that here the mean initial body weight was 101 Gm (range: 93-105 Gm.), and treatment was carried out without interruption for 94 days. At the end of this time, the clinical appearance of the rats was essentially the same as in the first series: no obvious difference between untreated controls and rats receiving AAN alone, but extreme skeletal lesions in the animals given AAN plus STH. On the 95th day, two rats of each group were killed for histologic study, while the remaining animals were left without treatment until the 128th day after initiation of the experiment. On the day treatment was discontinued the histologic changes in the bones and joints of the rats given STH in combination with AAN were essentially the same as in the first series, and no marked repair was noticeable after the recovery period of more than one month.

A rather singular change in this experiment was the splitting of the growth-cartilages (especially in the distal metaphysis of the femur) into several parallel plates. Such changes were quite exceptional in the first experiment, but in the second experiment they were present in the majority of the animals receiving AAN and STH (fig. 8).

## DISCUSSION

Under the conditions of our experiments, AAN alone produced only minor skeletal changes and no obvious derangements in the structure of the bone-marrow. On the other hand, combined treatment with AAN and STH resulted in marked skeletal deformities and transformation of hemopoietic into fatty bone-marrow. It has been amply demonstrated by previous work, including numerous observations in this Institute (6, 7), that under comparable conditions, STH alone produces gigantism but no such skeletal lesions as were found in these experiments. It seems therefore, that rats treated with AAN, at in themselves virtually ineffective dose levels, have been conditioned to certain otherwise not obtainable actions of STH.

In connection with the problem of aging, it is perhaps of some interest that many of the lesions induced by chronic combined treatment with AAN and STH resemble those normally seen in senescent rats. Among these changes are: 1) premature closure of the epiphyseal plates, 2) osteoporosis with dilatation of the blood-vessel channels in solid bone, 3) joint lesions reminiscent of osteoarthritis, 4) transformation of myeloid into fatty bone-marrow, and 5) excessive growth and enamel defects in incisor teeth.

It is also noteworthy that, although the mean initial body weight of the rats in all three groups of the main experiment was the same

(50 Gm.), the final body weight of the controls was 226 Gm. (range: 196-243 Gm.), that of the rats treated with AAN alone was 211 Gm. (range: 197-213 Gm.), and that of the rats receiving AAN in combination with STH was 178 Gm. (range: 139-196 Gm.). Furthermore, the long bones of the animals in Group III were obviously shorter than those of the other two groups. Thus the growth hormone actually inhibited both anabolism and growth in length, under these particular experimental conditions. In addition, the fur of the rats in Group I and II was normal and glossy, while that of the animals in Group III was shaggy, tended to fall out easily, and had lost its normal glossy sheen. The tendency towards catabolism and loss of hair is likewise characteristic of senile rats.

It is, of course, quite impossible to verify whether the syndrome observed here does actually correspond to premature aging; still it is not inconceivable, in the light of this work, that STH—which had already been shown to participate in the pathogenesis of many morbid lesions not primarily due to diseases of the endocrine glands—may also play a part in the process of normal senescence. Further work will be necessary to show whether toxic food products (not necessarily AAN itself) or toxic endogenous by-products of metabolism may, in synergism with endogenous STH, result in the development of changes usually ascribed to senility.

## SUMMARY

Experiments on rats indicate that moderate doses of aminoacetonitrile (AAN)—which in themselves elicit only minor lesions characteristic of bone-lathyrism—produce very pronounced morbid changes when administered in combination with a purified preparation of somatotrophic hormone (STH). Most important among these changes are: Premature closure of the epiphyseal plates, osteoporosis with dilatation of the blood-vessel channels in solid bone, joint lesions reminiscent of osteoarthritis, transformation of myeloid into fatty bone-marrow, excessive growth and enamel defects in the incisor teeth, loss of body weight, and shagginess of the fur with loss of its normal glossy sheen and a tendency to fall out.

These findings raise the question as to whether STH (perhaps in synergism with toxic food products or endogenous metabolites) may participate in the development of changes which are usually ascribed to senility.

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# THE LACTIC AND MALIC DEHYDROGENASE ACTIVITIES OF AORTIC AND PULMONARY ARTERY TISSUE IN INDIVIDUALS OF VARIOUS AGES*

J. R. MATZKE, M.D.,† J. E. KIRK, M.D., AND I. WANG, M.S.
*(From the Division of Gerontology, Washington University School of Medicine, St. Louis)*

The present study was undertaken with the purpose of determining the lactic and malic dehydrogenase activities of homogenates prepared from the aorta and pulmonary artery from individuals of various ages. In the case of the aortic samples the enzyme measurements were carried out both on apparently normal tissue portions and on arterial segments which were the site of arteriosclerotic changes.

## METHODS

Eighty-six samples of the human aorta (thoracic descending) and 77 samples of the pulmonary artery were obtained fresh at autopsy at the St. Louis City Morgue.‡ The age of the individuals from whom the samples were derived ranged between 0.2 and 83 years. Immediately after removal the samples were placed in sterile beakers immersed in ice.

Intima-media samples of normal and arteriosclerotic segments of the aorta and of the pulmonary artery were homogenized in a Pyrex grinder with 9 volumes of distilled water; the homogenizer was immersed in ice water during the homogenization.

Immediately before the enzyme activity measurements, 1 volume of the 10 per cent homogenate was diluted with 4 volumes of water and thoroughly mixed by brief stirring in a homogenizer. The resulting 2 per cent homogenate was employed for the enzyme determinations.

The lactic and malic dehydrogenase activities of the arterial homogenates were determined by a macro modification of Strominger and Lowry's (4) procedure. Twenty-five and 50 cu.mm. of 2 per cent homogenate were incubated at 38 C. with 6.0 ml. of substrate having a DPN concentration of 2 mM. An incubation period of 30 minutes was used for the 50 cu.mm. samples; in the case of the 25 cu.mm. samples readings were made both after 30 and 60 minutes' incubation. A high degree of proportionality was observed between the quantity of tissue employed and the enzyme activity values. In the experiments with the 25 cu.mm. homogenate samples a nearly linear relationship was found between time of incubation and recorded enzyme activities.

Determinations of tissue dry weight, nitrogen, and cholesterol content, and measurements of percentage areas of arteriosclerotic tissue were carried out as described in a previous publication (2).

## RESULTS

The results of the lactic and malic dehydrogenase determinations performed on the individual aortic and pulmonary samples and the mean values recorded for the various decades have been listed in table 1. The table further contains the observed dry weight, total nitrogen, and cholesterol values for the samples. In addition, the percentage values of the areas of the aortic samples which were the site of arteriosclerosis have been included.

### *Aortic Samples*

#### *I. Normal Aortic Tissue*

*Lactic Dehydrogenase*—The average quantity of lactate metabolized by the non-arteriosclerotic tissue samples (N = 81) was 1.02 mM/Gm. wet tissue/hour, and 28 mM/Gm. tissue nitrogen/hour. It will be seen from the data recorded in table 1 that a definite tendency was noted for the lactic dehydrogenase activity to increase until the age of 50 - 59 years, after which a decrease in the mean enzyme values was noted. The enzyme activity values calculated on the basis of the tissue nitrogen content in general showed the same variation with age as the values expressed per unit of wet tissue weight.

An analysis of the lactic dehydrogenase values recorded for the two sexes revealed that the mean enzyme activity of the samples derived from the women was 131 per cent of the values observed for the men in the corresponding age groups when expressed on the basis of wet tissue weight, and 129 per cent, when calculated on the basis of the tissue nitrogen content.

*Malic Dehydrogenase*—The mean quantity of l-malate metabolized by the 81 samples investigated was 0.53 mM/Gm. wet tissue/hour, and 14 mM/Gm. tissue nitrogen/hour. A calculation of the coefficient of correlation between age and malic dehydrogenase activity showed no significant change in enzyme activity with age:

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† St. Louis Heart Association Research Fellow.

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TABLE 1. LACTIC AND MALIC DEHYDROGENASE ACTIVITIES OF 86 HUMAN AORTIC SAMPLES AND 77 PULMONARY ARTERY SAMPLES.

| No. | Age (Years) | Sex, Race | NORMAL AORTIC TISSUE | | | | | | | ARTERIOSCLEROTIC AORTIC TISSUE | | | | | | | | PULMONARY ARTERY TISSUE | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | Dry Matter, % | Nitrogen, % of Wet Weight | Cholesterol, % of Wet Weight | Lactate Metabolized, mM/Gm. Wet Tissue/Hour | Lactate Metabolized, mM/Gm. Tissue N/Hour | Malate Metabolized, mM/Gm. Wet Tissue/Hour | Malate Metabolized, mM/Gm. Tissue N/Hour | Dry Matter, % | Nitrogen, % of Wet Weight | Cholesterol, % of Wet Weight | Lactate Metabolized, mM/Gm. Wet Tissue/Hour | Lactate Metabolized, mM/Gm. Tissue N/Hour | Malate Metabolized, mM/Gm. Wet Tissue/Hour | Malate Metabolized, mM/Gm. Tissue N/Hour | Area of Arteriosclerotic Tissue, in Percentage | Dry Matter, % | Nitrogen, % of Wet Weight | Cholesterol, % of Wet Weight | Lactate Metabolized, mM/Gm. Wet Tissue/Hour | Lactate Metabolized, mM/Gm. Tissue N/Hour | Malate Metabolized, mM/Gm. Wet Tissue/Hour | Malate Metabolized, mM/Gm. Tissue N/Hour |
| 1 | 0.2 | F C | 25.0 | | 0.2 | 0.40 | | 0.42 | | | | | | | | | | | | | 0.66 | | 0.64 | |
| 2 | 0.5 | M C | 34.7 | 4.98 | 0.2 | 0.21 | 5 | 0.35 | 8 | | | | | | | | | 29.4 | 3.98 | 0.2 | 0.92 | 23 | 0.44 | 11 |
| 3 | 0.6 | F C | 31.5 | 4.50 | 0.2 | 0.54 | 12 | 0.44 | 10 | | | | | | | | | 34.8 | 3.22 | 0.2 | 0.57 | 18 | 0.37 | 12 |
| 4 | 1 | F W | 32.6 | 5.63 | 0.2 | 0.86 | 15 | 0.54 | 10 | | | | | | | | | 36.7 | 5.16 | 0.2 | 0.69 | 13 | 0.55 | 11 |
| 5 | 1.5 | M C | 31.7 | 4.41 | 0.4 | 0.23 | 5 | 0.46 | 10 | | | | | | | | | 24.8 | 3.60 | 0.5 | 0.70 | 19 | 0.88 | 24 |
| 6 | 2 | M C | 36.9 | 4.88 | 0.2 | 0.58 | 12 | 0.44 | 9 | | | | | | | | | | | | | | | |
| 7 | 2 | M C | 30.9 | 4.65 | 0.3 | 0.34 | 7 | 0.40 | 9 | | | | | | | | | 31.2 | 4.35 | 0.2 | 0.40 | 9 | 0.29 | 7 |
| 8 | 3 | M W | 28.1 | 3.54 | 0.3 | 0.46 | 13 | 0.45 | 13 | | | | | | | | | | | | | | | |
| 9 | 4 | M W | 33.3 | 5.12 | 0.1 | 0.79 | 15 | 1.30 | 26 | | | | | | | | | | | | | | | |
| 10 | 4 | M C | 36.5 | 5.47 | 0.2 | 0.74 | 13 | 0.74 | 13 | | | | | | | | | | | | 0.32 | | 0.39 | |
| 11 | 4 | M C | 34.8 | 5.33 | 0.2 | 0.59 | 11 | 0.43 | 8 | | | | | | | | | 31.4 | 4.65 | 0.2 | 0.92 | 20 | 0.45 | 10 |
| | Mean..... | | 32.3 | 4.85 | 0.2 | 0.52 | 11 | 0.54 | 12 | | | | | | | | | 31.4 | 4.16 | 0.3 | 0.65 | 17 | 0.50 | 13 |
| 12 | 10 | M C | 33.4 | 4.66 | 0.2 | 0.64 | 14 | 0.74 | 16 | | | | | | | | | | | | | | | |
| 13 | 14 | M C | 31.3 | 4.04 | 0.2 | 0.67 | 17 | 0.85 | 21 | | | | | | | | | 24.5 | 3.11 | 0.2 | 1.22 | 39 | 0.68 | 22 |
| 14 | 17 | M W | 28.4 | 3.99 | 0.4 | 0.52 | 13 | 0.61 | 15 | 29.7 | 4.05 | 0.4 | 0.62 | 15 | 0.62 | 15 | 12 | 26.5 | 3.59 | 0.3 | 0.45 | 13 | 0.65 | 18 |
| 15 | 23 | F W | 33.2 | 4.02 | 0.4 | 0.38 | 9 | 0.36 | 9 | 29.6 | 3.76 | 0.5 | 0.74 | 20 | 0.50 | 13 | 13 | 29.1 | 3.90 | 0.4 | 0.47 | 12 | 0.75 | 20 |
| | Mean..... | | 31.6 | 4.18 | 0.3 | 0.55 | 13 | 0.64 | 15 | 29.7 | 3.90 | 0.5 | 0.68 | 18 | 0.56 | 14 | | 26.7 | 3.54 | 0.3 | 0.71 | 21 | 0.69 | 20 |
| 16 | 30 | F C | 27.7 | 3.70 | 0.5 | 2.02 | 55 | 0.66 | 18 | 29.9 | 3.86 | 0.8 | 0.91 | 24 | 0.65 | 17 | 45 | 24.3 | 3.12 | 0.3 | 1.00 | 32 | 1.07 | 34 |
| 17 | 31 | M W | | | | 0.85 | | 0.31 | | | | | | | | | 46 | | | | 0.61 | | | |
| 18 | 31 | F W | 37.6 | 4.98 | 0.3 | 1.75 | 35 | 0.41 | 8 | | | | | | | | | 24.4 | 3.15 | 0.3 | 1.24 | 39 | 0.71 | 28 |
| 19 | 33 | M W | 27.5 | 3.56 | 0.6 | 0.67 | 19 | 0.77 | 22 | 27.4 | 3.47 | 2.0 | 0.19 | 6 | 0.34 | 10 | 42 | | | | | | | |
| 20 | 33 | M C | 34.1 | 3.79 | 0.4 | 1.87 | 49 | 0.44 | 12 | | | | | | | | 1 | 22.6 | 2.93 | 0.2 | 0.88 | 30 | 0.64 | 22 |
| 21 | 34 | F W | 29.9 | 4.11 | 0.7 | 0.47 | 11 | 0.65 | 16 | | | | | | | | | 27.4 | 3.71 | 0.5 | 0.91 | 25 | 0.62 | 17 |
| 22 | 35 | F W | 32.5 | 4.39 | 0.4 | 1.14 | 26 | 0.48 | 11 | | | | | | | | | 27.6 | 2.64 | 0.3 | 1.17 | 44 | 0.50 | 19 |
| 23 | 35 | F W | 28.9 | 3.83 | 0.6 | 0.47 | 12 | 0.84 | 22 | 27.4 | 3.51 | 0.6 | 0.36 | 10 | 0.70 | 20 | 39 | 29.2 | 4.01 | 0.4 | 0.36 | 9 | 1.67 | 41 |
| 24 | 35 | F C | 32.5 | 4.64 | 0.3 | 0.68 | 15 | 0.51 | 11 | | | | | | | | 1 | 25.9 | 3.59 | 0.1 | 0.66 | 18 | 0.33 | 9 |
| 25 | 36 | M C | 30.3 | 4.42 | 0.6 | 2.31 | 52 | 0.91 | 21 | | | | 2.40 | | 0.75 | | 2 | 27.2 | 4.08 | 0.2 | 1.73 | 42 | 0.41 | 10 |
| 26 | 37 | F C | 27.3 | 3.53 | 0.7 | 0.74 | 21 | 0.40 | 11 | 26.8 | 3.29 | 1.2 | 0.93 | 28 | 0.34 | 10 | 11 | 23.8 | 3.34 | 0.3 | 0.74 | 22 | 0.66 | 20 |
| 27 | 38 | M C | 30.7 | 4.17 | 0.5 | 0.56 | 13 | 0.54 | 13 | | | | | | | | 6 | | | | | | | |
| 28 | 39 | F W | 27.2 | 3.60 | 0.2 | 0.88 | 24 | 0.41 | 11 | | | | | | | | | 23.9 | 3.35 | 0.2 | 0.52 | 16 | 0.46 | 14 |
| | Mean..... | | 30.5 | 4.06 | 0.5 | 1.11 | 28 | 0.56 | 15 | 27.9 | 3.54 | 1.2 | 0.96 | 17 | 0.56 | 14 | | 25.6 | 3.39 | 0.3 | 0.89 | 28 | 0.71 | 21 |
| 29 | 42 | M W | | | | | | | | 32.2 | 4.32 | 0.7 | 0.56 | 13 | 0.68 | 16 | 100 | 32.5 | 3.56 | 0.6 | 0.54 | 15 | 0.54 | 15 |
| 30 | 43 | M W | 30.2 | 4.24 | 0.6 | 0.36 | 9 | 0.80 | 19 | 30.3 | 4.09 | 1.5 | 0.71 | 17 | 0.32 | 8 | 10 | 29.4 | 3.87 | 0.2 | 0.67 | 17 | 0.43 | 11 |
| 31 | 44 | M W | 33.8 | 4.60 | 0.6 | 0.97 | 21 | 0.66 | 14 | | | 0.5 | 0.59 | | 0.37 | | 17 | | | | | | | |
| 32 | 44 | M C | 26.6 | 3.24 | 0.5 | 1.54 | 48 | 0.60 | 19 | 27.1 | 3.19 | 0.5 | 1.64 | 52 | 0.67 | 21 | 70 | 26.5 | 3.23 | 0.3 | 1.34 | 41 | 0.74 | 23 |
| 33 | 46 | M W | | | | 1.06 | | 0.61 | | | | | | | | | 95 | 27.8 | 3.71 | 0.3 | 0.74 | 20 | 0.74 | 20 |
| 34 | 46 | F W | 29.7 | 3.83 | 0.6 | 0.36 | 9 | 0.51 | 13 | 28.5 | 3.62 | 0.8 | 0.38 | 11 | 0.65 | 18 | 95 | 25.2 | 3.07 | 0.4 | 0.32 | 10 | 1.44 | 47 |
| 35 | 46 | F C | 31.7 | 4.16 | 0.5 | 1.52 | 37 | 0.38 | 9 | 38.6 | 4.15 | 1.4 | 1.32 | 32 | 0.45 | 11 | 50 | 26.1 | 3.54 | 0.3 | 1.25 | 35 | 0.51 | 14 |
| 36 | 46 | F C | 39.9 | 4.44 | 0.8 | 3.66 | 83 | 0.67 | 15 | 40.0 | 4.03 | 0.9 | 1.83 | 45 | 0.66 | 16 | 1 | 30.6 | 4.41 | 0.3 | 1.96 | 45 | 1.69 | 38 |
| 37 | 48 | M W | 28.6 | 3.85 | 0.5 | 1.37 | 36 | 0.64 | 17 | 29.4 | 2.83 | 1.2 | 1.27 | 42 | 0.44 | 16 | 27 | | | | | | | |
| 38 | 49 | F W | 27.7 | 3.32 | 0.7 | 1.68 | 51 | 0.63 | 19 | | | | | | | | | 31.7 | 3.21 | 0.3 | 0.91 | 28 | 0.51 | 16 |
| | Mean..... | | 31.1 | 3.97 | 0.6 | 1.40 | 37 | 0.61 | 16 | 32.3 | 3.75 | 0.9 | 1.04 | 30 | 0.53 | 15 | | 28.7 | 3.58 | 0.4 | 0.97 | 26 | 0.83 | 23 |
| 39 | 50 | M W | 24.3 | 3.05 | 0.8 | 2.06 | 67 | 0.59 | 19 | 25.5 | 2.97 | 0.9 | 1.46 | 49 | 0.58 | 20 | 24 | 24.5 | 3.10 | 0.3 | 1.84 | 59 | 0.68 | 22 |
| 40 | 50 | M W | | | | | | | | 26.5 | 2.71 | 1.2 | 1.14 | 42 | 0.48 | 18 | 43 | 30.7 | 3.72 | 0.4 | 1.17 | 32 | 0.50 | 13 |
| 41 | 50 | F C | 26.3 | 3.42 | 0.5 | 0.81 | 24 | 0.39 | 11 | 26.3 | 3.42 | 0.7 | 1.06 | 31 | 0.46 | 13 | 17 | 25.1 | 3.42 | 0.5 | 0.57 | 17 | 0.73 | 21 |
| 42 | 52 | M C | 30.3 | 4.05 | 0.2 | 0.31 | 8 | 0.44 | 11 | 30.2 | 4.13 | 1.2 | 0.28 | 7 | 0.29 | 7 | 37 | 24.9 | 2.85 | 0.4 | 1.02 | 36 | 0.80 | 28 |
| 43 | 53 | M W | 22.7 | 2.71 | 0.4 | 2.31 | 85 | 0.26 | 10 | 39.0 | 2.87 | 1.7 | 1.14 | 40 | 0.26 | 9 | 22 | 34.6 | 4.00 | 0.7 | 1.12 | 28 | 0.39 | 10 |
| 44 | 53 | M C | 29.7 | 4.18 | 0.7 | 1.18 | 28 | 0.58 | 14 | 31.6 | 3.77 | 1.5 | 1.43 | 38 | 0.70 | 19 | 15 | 27.6 | 3.93 | 0.4 | 0.94 | 24 | 0.49 | 13 |
| 45 | 54 | M W | 24.7 | 3.15 | 0.8 | 0.93 | 30 | 0.45 | 14 | 30.1 | 3.49 | 5.0 | 0.32 | 9 | 0.26 | 7 | 18 | 23.5 | 2.34 | 0.3 | 0.56 | 24 | 0.61 | 26 |

TABLE 1 (CONTINUED)

| No. | Age (Years) | Sex | Race | NORMAL AORTIC TISSUE | | | | | | | ARTERIOSCLEROTIC AORTIC TISSUE | | | | | | | | PULMONARY ARTERY TISSUE | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | Dry Matter, % | Nitrogen, % of Wet Weight | Cholesterol, % of Wet Weight | Lactate Metabolized, mM/Gm. Wet Tissue/Hour | Lactate Metabolized, mM/Gm. Tissue N/Hour | Malate Metabolized, mM/Gm. Wet Tissue/Hour | Malate Metabolized, mM/Gm. Tissue N/Hour | Dry Matter, % | Nitrogen, % of Wet Weight | Cholesterol, % of Wet Weight | Lactate Metabolized, mM/Gm. Wet Tissue/Hour | Lactate Metabolized, mM/Gm. Tissue N/Hour | Malate Metabolized, mM/Gm. Wet Tissue/Hour | Malate Metabolized, mM/Gm. Tissue N/Hour | Area of Arteriosclerotic Tissue, in Percentage | Dry Matter, % | Nitrogen, % of Wet Weight | Cholesterol, % of Wet Weight | Lactate Metabolized, mM/Gm. Wet Tissue/Hour | Lactate Metabolized, mM/Gm. Tissue N/Hour | Malate Metabolized, mM/Gm. Wet Tissue/Hour | Malate Metabolized, mM/Gm. Tissue N/Hour |
| 46 | 54 | M | C | 27.2 | 3.43 | 0.6 | 0.73 | 22 | 0.31 | 9 | 25.2 | 3.08 | 0.5 | 0.51 | 17 | 0.12 | 4 | 31 | 23.5 | 3.31 | 0.4 | 1.25 | 38 | 0.48 | 15 |
| 47 | 54 | F | W | 29.2 | 2.83 | 0.7 | 0.47 | 17 | 0.93 | 33 | 29.2 | 3.54 | 2.8 | 0.40 | 11 | 0.72 | 20 | 28 | 23.3 | 3.07 | 0.6 | 0.46 | 15 | 0.89 | 29 |
| 48 | 54 | F | C | 25.0 | 2.94 | 0.6 | 4.00 | 136 | 0.47 | 16 | 23.7 | 2.27 | 3.2 | 2.91 | 128 | 0.43 | 19 | 18 | 25.1 | 3.17 | 0.4 | 1.67 | 53 | 0.48 | 15 |
| 49 | 55 | M | W | 33.7 | 4.48 | 0.5 | 1.46 | 33 | 0.67 | 15 | 32.4 | 3.95 | 1.2 | 1.44 | 37 | 0.51 | 13 | 19 | 39.5 | 5.55 | 0.5 | 1.41 | 25 | 0.76 | 14 |
| 50 | 55 | M | W | 25.8 | 3.13 | 0.6 | 2.27 | 73 | 0.59 | 19 | 27.6 | 3.19 | 1.5 | 1.75 | 55 | 0.58 | 18 | 17 | 21.0 | 2.53 | 0.3 | 1.69 | 67 | 0.81 | 32 |
| 51 | 56 | M | W | 30.0 | 3.93 | 0.8 | 1.21 | 31 | 0.57 | 15 | 29.7 | 3.74 | 0.6 | 1.47 | 39 | 0.47 | 13 | 19 | 28.3 | 3.30 | 0.3 | 1.03 | 31 | 0.54 | 16 |
| 52 | 57 | M | W | | | | | | | | 29.3 | 2.84 | 1.7 | 0.93 | 33 | 0.27 | 10 | 78 | 19.3 | 2.61 | 0.4 | 0.76 | 29 | 0.54 | 21 |
| 53 | 59 | M | W | | | 0.7 | 1.54 | | 0.45 | | 27.8 | 3.60 | 4.5 | 0.59 | 16 | 0.34 | 9 | 47 | 27.2 | 3.73 | 0.3 | 0.60 | 16 | 0.48 | 13 |
| 54 | 59 | M | W | 28.5 | 2.98 | 1.3 | 2.06 | 69 | 0.59 | 20 | 39.2 | 1.16 | 2.1 | 1.46 | 126 | 0.58 | 50 | 24 | 24.8 | 3.04 | 0.5 | 1.84 | 61 | 0.68 | 22 |
| | Mean..... | | | 27.5 | 3.40 | 0.7 | 1.53 | 48 | 0.52 | 16 | 29.5 | 3.17 | 1.9 | 1.14 | 42 | 0.44 | 15 | | 26.4 | 3.36 | 0.4 | 1.12 | 35 | 0.62 | 19 |
| 55 | 60 | M | W | 28.8 | 3.91 | 0.5 | 1.07 | 27 | 0.52 | 13 | 23.9 | 3.09 | 1.8 | 0.81 | 26 | 0.35 | 11 | 36 | 24.0 | 3.18 | 0.5 | 1.51 | 48 | 0.53 | 17 |
| 56 | 60 | M | W | 25.9 | 3.19 | 0.7 | 0.41 | 13 | 0.33 | 10 | 25.6 | 2.82 | 2.9 | 0.24 | 9 | 0.24 | 9 | 93 | 19.3 | 2.61 | 0.5 | 0.53 | 20 | 0.92 | 35 |
| 57 | 60 | F | W | 28.5 | 3.29 | 1.2 | 0.95 | 29 | 0.30 | 9 | 44.6 | 2.23 | 3.3 | 0.83 | 37 | 0.29 | 13 | 23 | 27.3 | 3.60 | 1.3 | 0.68 | 19 | 0.39 | 11 |
| 58 | 61 | M | W | 28.6 | 3.80 | 0.4 | 0.78 | 21 | 0.40 | 11 | 33.2 | 4.11 | 2.9 | 0.33 | 8 | 0.23 | 6 | 32 | 23.3 | 3.17 | 0.3 | 0.79 | 25 | 0.42 | 13 |
| 59 | 61 | M | W | 30.8 | 3.82 | 0.9 | 0.84 | 22 | 0.42 | 11 | 26.3 | 1.77 | 1.5 | 0.55 | 31 | 0.47 | 27 | 50 | 25.3 | 3.26 | 0.6 | 1.73 | 53 | 0.60 | 18 |
| 60 | 62 | M | W | 29.0 | 3.71 | 0.8 | 1.06 | 29 | 0.46 | 12 | 26.5 | 3.25 | 2.2 | 0.88 | 27 | 0.36 | 11 | 14 | 25.9 | 3.67 | 0.8 | 1.00 | 27 | 0.56 | 15 |
| 61 | 62 | M | C | 32.1 | 3.75 | 0.5 | 0.22 | 6 | 0.44 | 12 | 39.5 | 2.79 | 5.1 | 0.24 | 9 | 0.24 | 9 | 35 | 23.2 | 2.81 | 0.5 | 0.84 | 30 | 0.61 | 22 |
| 62 | 62 | F | W | 33.6 | 3.34 | 0.9 | 1.38 | 42 | 0.66 | 20 | 37.5 | 1.73 | 1.6 | 0.98 | 56 | 0.52 | 30 | 34 | 29.1 | 4.07 | 0.5 | 1.61 | 40 | 2.63 | 65 |
| 63 | 63 | M | W | 28.5 | 3.87 | 0.7 | 0.95 | 25 | 0.53 | 14 | 29.8 | 3.34 | 1.5 | 1.01 | 30 | 0.42 | 13 | 5 | 26.7 | 3.75 | 0.5 | 0.47 | 13 | 0.48 | 13 |
| 64 | 63 | M | W | 30.7 | 3.81 | 1.2 | 1.30 | 34 | 0.77 | 20 | 32.8 | 5.43 | 2.1 | 0.66 | 16 | 0.47 | 9 | 98 | 25.8 | 3.52 | 1.1 | 1.47 | 42 | 0.51 | 15 |
| 65 | 63 | M | W | 24.0 | 3.03 | 0.6 | 0.42 | 14 | 0.24 | 8 | 31.0 | 2.43 | 0.7 | 0.37 | 15 | 0.25 | 10 | 72 | 25.2 | 3.19 | 0.5 | 0.52 | 16 | 0.34 | 11 |
| 66 | 63 | M | C | 26.2 | 4.66 | 1.3 | 0.30 | 6. | 0.46 | 10 | 28.2 | 3.06 | 1.1 | 0.20 | 6 | 0.52 | 17 | 91 | 21.6 | 3.00 | 0.6 | 0.21 | 7 | 0.43 | 14 |
| 67 | 64 | M | W | 25.5 | 3.48 | 0.5 | 1.78 | 51 | 0.48 | 14 | 28.6 | 2.80 | 2.9 | 1.60 | 57 | 0.66 | 24 | 19 | 22.7 | 3.31 | 0.3 | 1.10 | 33 | 0.52 | 16 |
| 68 | 64 | M | W | | | | | | | | 31.7 | 3.34 | 0.6 | 0.23 | 7 | 0.26 | 8 | 100 | 21.0 | 2.85 | 0.4 | 0.76 | 27 | 0.54 | 19 |
| 69 | 64 | M | W | 28.4 | 3.21 | 0.7 | 1.05 | 33 | 0.50 | 16 | 29.5 | 2.58 | 3.0 | 1.25 | 49 | 0.40 | 16 | 78 | 23.3 | 2.92 | 0.6 | 0.91 | 31 | 0.73 | 25 |
| 70 | 64 | M | W | 29.2 | 3.89 | 0.9 | 1.10 | 28 | 0.55 | 14 | 33.1 | 3.63 | 4.0 | 0.74 | 19 | 0.56 | 14 | 39 | 27.0 | 3.77 | 0.9 | 0.63 | 17 | 0.41 | 11 |
| 71 | 64 | M | C | 30.7 | 3.71 | 0.5 | 1.01 | 27 | 0.38 | 10 | | | | | | | | | 28.2 | 3.80 | 0.3 | 0.60 | 16 | 0.46 | 12 |
| 72 | 65 | M | W | | | | | | | | 27.8 | 3.71 | 1.4 | 0.53 | 14 | 0.34 | 9 | 100 | 21.3 | 2.93 | 0.3 | 1.05 | 36 | 0.59 | 20 |
| 73 | 65 | M | W | 29.7 | 2.54 | 0.7 | 0.83 | 33 | 0.51 | 20 | 33.1 | 2.93 | 5.5 | 0.35 | 12 | 0.24 | 8 | 51 | 25.0 | 3.16 | 0.5 | 0.84 | 27 | 0.50 | 16 |
| 74 | 66 | M | W | 30.7 | 3.49 | 1.6 | 1.36 | 39 | 0.39 | 11 | 42.1 | 1.88 | 3.8 | 0.75 | 40 | 0.41 | 22 | 36 | 24.3 | 3.08 | 0.4 | 1.07 | 35 | 0.36 | 12 |
| 75 | 67 | M | W | 32.8 | 3.91 | 1.0 | 0.70 | 18 | 0.49 | 13 | 38.4 | 3.97 | 3.8 | 0.34 | 9 | 0.25 | 6 | 91 | 27.8 | 3.76 | 0.7 | 0.67 | 18 | 0.48 | 13 |
| 76 | 67 | M | W | 30.9 | 3.81 | 1.1 | 0.41 | 11 | 0.44 | 12 | 35.2 | 2.88 | 3.2 | 0.21 | 7 | 0.30 | 10 | 18 | | | | | | | |
| 77 | 69 | M | W | 29.3 | 3.82 | 0.9 | 0.47 | 12 | 0.42 | 11 | 33.0 | 3.40 | 1.4 | 0.20 | 6 | 0.42 | 12 | 42 | 24.1 | 3.10 | 0.5 | 0.40 | 13 | 0.40 | 13 |
| 78 | 69 | M | W | 27.1 | 5.50 | 0.8 | 0.77 | 14 | 0.29 | 5 | 26.2 | 3.30 | 1.7 | 0.36 | 11 | 0.22 | 7 | 29 | 25.9 | 3.59 | 0.3 | 0.47 | 13 | 0.34 | 10 |
| 79 | 69 | M | W | 26.3 | 3.68 | 0.7 | 0.95 | 26 | 1.05 | 29 | 29.3 | 4.09 | 0.6 | 0.97 | 24 | 0.42 | 10 | 29 | 29.2 | 4.18 | 0.3 | 0.74 | 18 | 0.52 | 12 |
| 80 | 69 | M | W | 30.1 | 3.92 | 0.7 | 0.62 | 16 | 0.42 | 11 | | | | | | | | 17 | 29.1 | 3.90 | 0.5 | 0.57 | 15 | 0.43 | 11 |
| | Mean..... | | | 29.1 | 3.72 | 0.8 | 0.87 | 24 | 0.48 | 13 | 31.9 | 3.11 | 2.5 | 0.61 | 22 | 0.37 | 13 | | 25.0 | 3.37 | 0.6 | 0.85 | 26 | 0.59 | 17 |
| 81 | 71 | M | W | 29.2 | 3.44 | 0.7 | 0.22 | 6 | 0.51 | 15 | 30.7 | 3.01 | 5.9 | 0.31 | 10 | 0.23 | 8 | 15 | 25.2 | 3.16 | 0.5 | 0.21 | 7 | 0.24 | 8 |
| 82 | 72 | M | W | 30.4 | 3.95 | 1.4 | 1.04 | 26 | 0.51 | 13 | 33.4 | 2.92 | 5.5 | 0.81 | 28 | 0.45 | 15 | 38 | 23.0 | 3.02 | 1.7 | 1.09 | 36 | 0.55 | 18 |
| 83 | 75 | F | W | 28.9 | 3.37 | 0.7 | 1.34 | 39 | 0.32 | 10 | 44.4 | 1.57 | 2.2 | 0.32 | 20 | 0.15 | 10 | 41 | 21.1 | 2.29 | 0.6 | 0.49 | 21 | 0.36 | 16 |
| 84 | 78 | F | C | 32.2 | 2.71 | 0.9 | 0.45 | 17 | 0.53 | 20 | 36.3 | 4.20 | 8.3 | 0.35 | 8 | 0.34 | 8 | 35 | 21.9 | 2.77 | 0.8 | 0.24 | 9 | 0.40 | 15 |
| | Mean..... | | | 30.2 | 3.36 | 0.9 | 0.76 | 22 | 0.47 | 15 | 36.2 | 2.93 | 5.5 | 0.45 | 17 | 0.29 | 10 | | 22.9 | 2.81 | 0.9 | 0.51 | 18 | 0.39 | 14 |
| 85 | 81 | F | W | 29.9 | 3.09 | 1.3 | 0.88 | 28 | 0.31 | 10 | 35.0 | 1.09 | 4.5 | 0.58 | 53 | 0.29 | 27 | 30 | 24.5 | 2.54 | 0.7 | 1.02 | 40 | 0.36 | 14 |
| 86 | 83 | M | W | 28.9 | 3.53 | 0.8 | 0.49 | 14 | 0.39 | 11 | 32.4 | 4.46 | 1.2 | 0.46 | 10 | 0.33 | 7 | 42 | 23.2 | 3.19 | 0.2 | 0.77 | 24 | 0.43 | 13 |
| | Mean..... | | | 29.4 | 3.31 | 1.1 | 0.69 | 21 | 0.35 | 11 | 33.7 | 2.78 | 2.9 | 0.52 | 31 | 0.31 | 17 | | 23.9 | 2.86 | 0.5 | 0.89 | 32 | 0.40 | 14 |
| Grand Mean..... | | | | 29.9 | 3.89 | 0.6 | 1.02 | 28 | 0.53 | 14 | 31.3 | 3.23 | 2.2 | 0.83 | 28 | 0.43 | 14 | | 26.3 | 3.42 | 0.4 | 0.88 | 27 | 0.61 | 18 |

Age/quantity of l-malate metabolized/Gm. wet tissue:
$r = -0.20$ ($t = 1.81$, $N = 81$)
Age/quantity of l-malate metabolized/Gm. tissue nitrogen:
$r = +0.04$ ($t = 0.35$, $N = 77$)

The malic dehydrogenase activity of the samples derived from the women was 97 per cent of that found for the men, when expressed on the basis of wet tissue weight, and 100 per cent, when calculated on the basis of the tissue nitrogen content.

*II. Arteriosclerotic Aortic Tissue*

Determinations of the lactic and malic dehydrogenase activities of arteriosclerotic tissue were made on 61 samples; in 55 of these samples sufficient normal arterial tissue was available to permit determinations also on the normal portions of the vessel wall.

In table 2 the average enzyme values of 51 arteriosclerotic samples for the age groups 30-83 years have been recorded for the various decades in percentages of the values found for the normal tissue. It will be seen from the table that significantly lower lactic dehydrogenase values were observed for the 50-69-year age group when the enzyme activities were expressed on the basis of wet tissue weight; in the case of malic dehydrogenase a significant difference was noted for the samples from the 60-83 year old subjects. In contrast to this no significant differences between the mean lactic and malic dehydrogenase activities of the normal and arteriosclerotic tissue were found when the values were calculated on the basis of the tissue nitrogen content.

TABLE 2. MEAN ENZYME ACTIVITIES OF ARTERIOSCLEROTIC TISSUE EXPRESSED IN PERCENTAGE OF ACTIVITIES OF NORMAL TISSUE OF THE SAME AORTIC SAMPLES.

| Age Group (Years) | Lactic Dehydrogenase | | | | Malic Dehydrogenase | | | |
|---|---|---|---|---|---|---|---|---|
| | Wet Tissue | | | Tissue Nitrogen | Wet Tissue | | Tissue Nitrogen | |
| | N | % | t of diff. | % t of diff. | % | t of diff. | % | t of diff. |
| 30 - 49 | 10 | 91 | 1.53 | 97 1.20 | 86 | 1.32 | 94 | 1.03 |
| 50 - 59 | 13 | 84 | 2.54 | 95 0.43 | 87 | 0.63 | 100 | 0.00 |
| 60 - 69 | 22 | 72 | 5.50 | 93 0.67 | 81 | 2.80 | 108 | 0.03 |
| 70 - 83 | 6 | 80 | 1.55 | 105 0.08 | 70 | 2.23 | 107 | 0.16 |

*Pulmonary Artery Samples*

*Lactic Dehydrogenase*—The average quantity of lactate metabolized by the pulmonary artery samples ($N = 77$) was 0.88 mM/Gm. wet tissue/hour, and 27 mM/Gm. tissue nitrogen/hour. The mean values found for the women were, respectively, 94 and 89 per cent of those observed for the men. As in the case of the aortic samples a tendency was noted for the enzyme activity of the tissue to increase until the age of 50-59 years, after which a decrease in the average values occurred.

*Malic Dehydrogenase*—The mean quantity of l-malate metabolized by the pulmonary artery samples ($N = 76$) was 0.61 mM/Gm. wet tissue/hour, and 18 mM/Gm. tissue nitrogen/hour. A calculation of the coefficient of correlation between age and malic dehydrogenase activity showed no significant variation in enzyme activity with age:

Age/quantity of l-malate metabolized/Gm. wet tissue:
$r = -0.07$ ($t = 0.60$, $N = 76$)
Age/quantity of l-malate metabolized/Gm. tissue nitrogen:
$r = -0.02$ ($t = 0.17$, $N = 74$)

The malic dehydrogenase activity of the samples derived from the women was 139 per cent of that observed for the men, both when calculated on the basis of wet tissue weight and tissue nitrogen content.

## DISCUSSION

The average lactic and malic dehydrogenase activities observed for normal human aortic tissue are, respectively, about 22 and 3.5 per cent of the values reported by Strominger and Lowry (4) for the cortex of the rabbit brain. The increase observed in lactic dehydrogenase activity of both aortic and pulmonary artery tissue with age until about 50-59 years with a subsequent decrease in activity in later decades resembles the findings previously reported from this laboratory (3) for beta-glucuronidase. A similar behavior has been found for some enzyme systems of other organs, as recently reviewed by Barrows (1).

Although a notable difference in the mean enzyme activities of normal and arteriosclerotic aortic tissue was observed in samples derived from older individuals when expressed on the basis of wet tissue weight, no significant differ-

ence in the average activities was found when the values were calculated on the basis of the tissue nitrogen content.

SUMMARY

Determinations were made of the lactic and malic dehydrogenase activities of homogenates of 86 samples of the human aorta and 77 samples of the pulmonary artery, derived from individuals aged 0.2 to 83 years. In the case of the aortic samples the enzyme measurements were carried out both on normal and arteriosclerotic areas of the vessel wall. The determinations were performed by a macromodification of Strominger and Lowry's procedure.

The average quantities of lactate metabolized by the normal and arteriosclerotic aortic tissue were, respectively, 1.02 and 0.83 mM/Gm. wet tissue/hour. For the pulmonary artery samples a mean value of 0.88 mM was observed. The corresponding values for the malate utilization by the arterial tissue were 0.53, 0.43, and 0.61 mM.

The lactic dehydrogenase activity of both the aortic and pulmonary artery samples was found to increase until the age of 50-59 years, after which a decrease in the average values occurred. No significant change with age in the malic dehydrogenase activity of the samples was observed.

Although the enzyme activities of the wet arteriosclerotic tissue frequently were found to be lower than the activities of the normal sections of the aortic wall no significant difference in the mean values were found when the activities were expressed on the basis of the tissue nitrogen content.

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# A STUDY OF AGE DIFFERENCES IN THE X-RAY DENSITY OF FIVE BONES IN THE ADULT HUMAN WRIST AND HAND*

DONALD MAINLAND, Sc.D.

*(From the Department of Medical Statistics and the Study Group on Rheumatic Diseases, New York University College of Medicine, New York, New York†)*

A study (2) of the calcaneus in symptom-free Canadian men, from 20 to 84 years old, revealed no significant correlation between age and x-ray density, expressed as thickness of an aluminum wedge exposed on the same film. A plausible explanation was that the calcaneus is subjected to body weight throughout life; and therefore it seemed desirable to examine a region where this factor is absent. Few regions, however, are suitable for such study, because, to avoid gridlines, table-top exposure is necessary, and therefore, to minimize the effects of secondary radiation, the part x-rayed must be fairly thin. The choice is further limited by the need to avoid overlapping of bone shadows and to avoid bones with very irregular or angled surfaces, because uncontrollable differences in the positioning of such bones, in the same or different subjects, can increase the observational error greatly. For these reasons, among the parts that do not support the body, the hand is the most suitable, and it was chosen for the present study, conducted on the same subjects, by the same observers, and by the same methods, as the calcaneus study (2), where details of technique can be found, along with a discussion of sources of bias in such cross-sectional surveys.

As with the calcaneus, a search for age differences has entailed the study of differences between replicate readings of the same film, replicate visits, right and left sides, males and females, and different subjects of the same age.

## METHODS

*Subjects.*—The subjects were 50 Canadian white men (students, professional and business men, aged 20 to 84) and 12 women in the same classes (aged 19 to 30), without history or current evidence of bone or joint disease.* Thirty-eight of the men, available for physiologic tests, showed typical age differences in blood pressure, auditory and visual acuity, visual accommodation and hand grip (4).

*Roentgenography.*—The roentgenograms (on 10 × 12 in. no-screen films with table-top exposure) were made at the same time as the foot films for the calcaneus study. The focal spot, at 6 feet above the table, was centered on the middle of the metacarpal region to produce a postero-anterior film. Exposure factors: 100 ma., 0.3 sec., kv.p. usually 70, but varying from 68 to 72 according to the thickness of the hand. The same aluminum step-wedge was used as for the calcaneus. To provide bone thickness measurements, a latero-medial film (with the ulnar side of the hand on the film holder) was also prepared.

*Densitometry.*—The bones examined were the distal part of the shaft of the radius, the lunate, capitate, shaft of metacarpal V, and shaft of the middle phalanx of the fifth finger. The choice was determined by three considerations: (a) The desire to concentrate chiefly on bones investigated by Mack and her collaborators (1) who have done extensive work on bone densitometry, (b) The desire to avoid possibly useless labor, e.g., by examining more than one finger, (c) The need to restrict the densitometry time on any one film to less than 10 minutes, in accordance with strict operating rules (3).

For photometry, by Photovolt transmission densitometer, outlines of the bones in the postero-anterior films were drawn on tracing paper clipped to the protective cellulose envelope containing the film. Then, to assist in the location of points for density measurement, a paper with black-ruled squares of ½ cm. sides was placed behind the tracings. At 1 cm. above the upper

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† Address: 550 First Avenue, New York 16, N. Y.

* A man with Dupuytren's contracture was, of course, excluded from the hand study because he could not place his fingers flat on the film.

(proximal) end of the radio-ulnar joint a transverse line on the radius was divided into 4 equal parts, to give 3 reading points, whose aluminum density equivalents were averaged in the analysis. On the same transverse line, near to the medial and lateral sides of the radius, soft tissue readings were taken. On each of the 4 other bones, the density was read at the central point, as judged by the eye with the aid of the squared paper. For the metacarpal and phalanx, soft tissue densities were read close to the medial sides of the middle of the bones. On the aluminum wedge the densities of the first 10 steps were recorded.

*Concomitant Variates.*—On each visit of each subject, besides stature and weight, a reading of the "external carpal thickness" was made by an obstetric pelvimeter with its points placed with moderate pressure against the front and back of the central region of the carpus, and then applied to a steel millimeter rule.

The latero-medial films did not consistently give views of the radius, capitate, and the two finger bones suitable for measurement of thickness (antero-posterior axis), but the anterior and posterior margins of the lunate were drawn on tracing paper (by D.M.) and the distance between them at the middle of the bone was measured (by H.H.W.). The same method was used on the head of the ulna, as a substitute for thickness of the radius, with which it is necessarily correlated to some degree.

As another possible substitute for bone thickness, the widths (transverse axes) of the head of the ulna, the lunate, capitate, and the two finger bones (at their central points) were measured (by H.H.W.) on the tracings of the postero-anterior films.

*Correction for Differences in Soft Tissue Density and Bone Thickness.* — For this correction, the regression of bone density on soft tissue density was used, as in the calcaneus study. In correcting the lunate and capitate densities the soft tissue medial to the radius was taken as the best available estimate.

*Analysis of Data.*—Except in the comparison of the two independent rounds of density readings (on a separate tracing in each round), the mean of the first and second rounds was used in all analyses. The same analytic methods were used as on the calcaneus data, and when a probability (P) value is not specified in the report, the 5 per cent level of significance is implied.

In comparing results from different hand bones, it must be remembered that the 5 bones are not independent, for all the bones of any particular hand are not only in the same person but on the same film. They cannot provide independent confirmation of any finding; but if the differences between estimates from the 5 bones are significant, i.e., greater than is attributed to chance variation among *independent* samples, the verdict of significance can be safely accepted.

For comparison with the calcaneus, some of the values found in that bone (2) are repeated in this report.

## RESULTS

### *Differences between Densitometer Readings*

The inter-round differences represented variable reading error, expressible as the standard deviation (SD) of the difference between two estimates from the same film. Range of SD's (in mm. aluminum), each from 122 films: metacarpal, 0.124; lunate, 0.216; (calcaneus, 0.195). Because all 5 bones were on the same film, some correlation between their reading errors might be expected, but Bartlett's test for heterogeneity of variance (5) showed that the errors differed significantly (P very small).

### *Differences between Right and Left Hands*

In 32 men the right hand had been x-rayed on one visit, the left hand on the other (16 RL's and 16 LR's). Even after correction for soft tissue density differences, each bone showed a positive mean R-L density difference (in mm. aluminum): radius, +0.239; lunate, +0.096; capitate, +0.270; metacarpal, +0.182; phalanx, +0.128. All the differences were significant (P less than 0.001) except in the lunate ($P = 0.2 - 0.1$). In the calcaneus the density difference was significant, but the left bone was denser than the right.

No adjustment for bone thickness was appropriate, because there was no significant correlation between density difference and difference in the linear measurements on the two sides. Unfortunately, information on the right- or lefthandedness of the subjects had not been obtained.

*Differences between Visits of the Same Person*

The 16 men whose right (or left) hand was x-rayed on both visits provided estimates of random intervisit variation in bone density, after regression of bone density difference on soft tissue density difference (range of r values; phalanx, +0.834; metacarpal, +0.958). The standard deviations representing variation from regression were estimated, and, although the samples were small, ± 2SD indicated roughly what allowance would be necessary before asserting, with 95 per cent probability, that a particular observed intervisit bone density difference was due to something more than technique (positioning, x-raying, processing, or densitometry).

The 2SD values (in mm. aluminum, with percentages of respective mean bone densities) were: radius, 0.500 (8.8); lunate, 0.874 (14.9); capitate, 0.833 (15.1); metacarpal, 0.291 (8.5); phalanx, 0.327 (15.3); (calcaneus, 0.468 (6.2)). The 5 bones differed significantly in their intervisit variation (P very small) and seemed to fall into 3 groups, in ascending order of SD: metacarpal and phalanx, radius (average of 3 reading points), capitate, and lunate. As in the calcaneus, the inter-reading variation accounted for only a small part of the intervisit variation.

*Differences between Subjects*

The 41 men who each provided a film of the right hand showed the following mean densities (in mm. aluminum): radius, 5.689; lunate, 5.683; capitate, 5.393; metacarpal, 3.326; phalanx, 2.096; (calcaneus (left), 7.741).

In order to discover the most effective methods of reducing intersubject variation, the correlations between bone density and the following variates were estimated: soft tissue, bone size, stature, and weight.

*Correlation with Soft Tissue Density.*—The mean soft tissue densities (in mm. aluminum) in these 41 men were: medial to radius, 3.877; lateral to radius, 2.070; medial to metacarpal, 1.565; medial to phalanx, 0.564.

Range of r values for bone density and soft tissue density: radius (lateral soft tissue), +0.558; metacarpal, +0.832. For correction of radius density, the medial soft tissue density (r = +0.752) was used.

Range of linear regression coefficients, representing the average increase of bone density (in mm. aluminum) per millimeter increase in soft tissue density: lunate, 0.640; metacarpal, 1.184; (calcaneus, 1.037). There was no suggestion of a curvilinear relationship.

*Correlation with Bone Size.*—There was no significant correlation between bone densities and linear dimensions on either the postero-anterior or the latero-medial films, although all the coefficients were positive. The highest r value was + 0.283 (P = 0.1 – 0.05) for lunate density and its antero-posterior axis. It was noteworthy, also, that when the same bones, head of ulna and lunate, were measured on latero-medial and postero-anterior films, the correlations between the two dimensions were low—head of ulna, +0.121 (P = 0.5 – 0.4); lunate, +0.297 (P = 0.1 – 0.05).

The external antero-posterior thickness of the carpus, measured directly on the subjects, was correlated with the densities of the radius, lunate, and capitate (r = +0.45 to +0.51; P less than 0.01), but this measurement depends considerably on soft tissue thickness, and elimination of soft tissue density by partial correlation reduced the correlation with bone density to a nonsignificant value (+0.27 for radius; P = 0.1 approx.).

In summary, none of the linear dimensions obtained in the hand region, either on films or on the subjects, provided an effective means of reducing intersubject variation in bone density.

*Correlations with Stature and Weight.*—The correlations between bone density and stature were not significant—radius, +0.081 (P = 0.7—0.6); lunate, +0.280 (P = 0.1 – 0.05).

Correlations of bone density with body weight were, however, positive and significant for all 5 bones. Range of r values: radius, +0.425 (P = 0.01 – 0.001); capitate, +0.510 (P less than 0.001); (calcaneus, +0.465).

Correlations between weight and soft tissue density were also positive, significant, and of similar magnitude to those between weight and bone density. Hence, after elimination of soft tissue density by partial correlation the r's for weight and bone density of all the bones, except the phalanx, were not significant—range: metacarpal, +0.186 (P = 0.3 – 0.2); capitate, +0.308 (P = 0.05 approx.); (calcaneus, +0.247; P = 0.2 – 0.1). For the phalanx, however, the correlation remained significant, +0.360 (P = 0.02 approx.). (Correlations between bone size, stature and weight were examined for head of ulna, metacarpal, and phalanx, and were found below 0.1; P = 0.7 or greater).

### *Age Relationships*

Age relationships were studied in the 41 men whose right hands were x-rayed. The frequency distribution of ages covered the whole range from 20 to 84, and was almost identical with those of the men whose left calcaneus was studied (2), but the right hands were chosen instead of the left because they provided a film from an additional subject.

Bone dimensions showed no significant correlation with age. Range of r values: metacarpal, +0.270 (P = 0.1–0.05); lunate, +0.163 (P = 0.4–0.3).

The weight-age relationship was also nonsignificant (r = −0.127; P = 0.5 – 0.4). Stature was negatively correlated with age (r = −0.442; P = 0.01–0.001), but its low correlation with bone density made it an ineffective correction factor for the age-density relationship.

Correlation coefficients for bone density and age, before correction for soft tissue or other variates, were: radius, −0.372 (P = 0.02–0.01); lunate, −0.121 (P = 0.5–0.4); capitate, −0.115 (P = 0.5–0.4); metacarpal, −0.157 (P = 0.4–0.3); phalanx, −0.337 (P = 0.05–0.02); (calcaneus, −0.035).

All 4 soft tissue densities were negatively correlated with age, but the only significant r value was found in the soft tissue medial to the radius (−0.388; P = 0.02–0.01). Of the other 3, the highest was −0.163 (P = 0.4–0.3) in the metacarpal soft tissue.

After elimination of soft tissue by partial correlation the r values for bone density and age were: radius, −0.132 (P = 0.5–0.4); lunate, +0.103 (P = 0.6–0.5); capitate, +0.120 (P = 0.5–0.4); metacarpal, −0.050 (P = 0.8 – 0.7); phalanx, −0.431 (P = 0.01 – 0.001); (calcaneus, +0.227; P = 0.2–0.1).

The age relationship of the phalanx density, therefore, is the only one that is significant, and it was only slightly changed (to r = −0.414) by adjustment for body weight as well as soft tissue. The regression for phalanx density on weight, independent of soft tissue and age, was significant (P = 0.05–0.02), and it is therefore shown in the following equation, where BD = bone density of the phalanx (mm. aluminum), STD = soft tissue density medial to the phalanx, A = age to the nearest year, W = weight in pounds.

$$BD = 1.296 + 0.971\ STD - 0.00535\ A + 0.00340\ W.$$

The regression coefficients show that bone density differences had an almost millimeter-per-millimeter relationship with soft tissue density differences, whereas age and weight differences were only slightly reflected in the bone density. By taking the relationships as linear and recalling the mean density of the phalanx (2.096 mm.) some approximate average differences can be estimated: a diminution of about 1/10 mm. density per 20 years of additional age (5 per cent of the mean density), and an increase of about 1/15 mm. density per 20 pounds of additional weight (3.25 per cent of the mean density).

Estimation of confidence limits (95 per cent) for these regression coefficients, from twice their standard deviations, showed that in a population randomly represented by these 41 men the average differences associated with age and weight would be unlikely to exceed a loss of 0.185 mm. density per 20 years (8.8 per cent of the sample mean) or a gain of 0.131 mm. per 20 pounds (6.3 per cent of the sample mean). Similar information regarding the age relationships of other bones is shown in table 1. (for the calcaneus, confidence limits for the 20-year age difference, expressed as percentages of the mean density, were −0.8 per cent and +4.4 per cent.)

### *Relationship of Bone Density to Degeneration of Joints*

Films from the older men showed the customary signs of aging in the interphalangeal joints—flattening of articular surfaces, diminution of joint spaces, and angularity (with occasional lipping) at the articular margins—which are better entitled "age degeneration" than

TABLE 1. ESTIMATED AVERAGE AGE DIFFERENCES IN BONE DENSITY AFTER CORRECTION FOR SOFT TISSUE DENSITY BY LINEAR REGRESSION (41 MEN). (Densities are in mm. aluminum.)

| Bone | Mean Density in Sample | Slope of Regression (mm./Yr.) | Probability (P) | Confidence Limits (95%) of Loss (−) or Gain (+) per 20 Years, Expressed as Percentage of Sample Mean | |
|---|---|---|---|---|---|
| Radius..... | 5.689 | −0.00305 | 0.5—0.4 | −3.7 | +1.6 |
| Lunate..... | 5.683 | +0.00249 | 0.6—0.5 | −2.0 | +3.7 |
| Capitate... | 5.393 | +0.00288 | 0.5—0.4 | −1.6 | +3.7 |
| Metacarpal. | 3.326 | −0.000386 | 0.8—0.7 | −2.2 | +1.7 |
| Phalanx*... | 2.096 | −0.00535 | <0.01 | −8.8 | −1.4 |

* Corrected for weight-density correlation as well as for soft tissue.

"osteo-arthritis." The question now arose: Was the negative correlation of bone density with age simply due to the greater frequency (and greater degree) of articular degeneration among the older men? If that were so, the age relationship of bone density from 20 to 84 years would be best represented, not by a straight line, but by a curve, fairly horizontal in the earlier decades and descending in the older men. A simple test for such curvilinearity is the introduction into the regression equation of the square of age, and, when this was done, there was no significantly better fit of the observed bone density values than was provided by the regression equation given above, which contains age but not the square of age.

The relationship between bone density and articular degeneration was studied more directly by an attempt to express objectively the degree of degeneration in the right-hand films of the 12 oldest men (ages 66 to 84). The assessor (DM), working without knowledge of the actual ages represented by the individual films, arranged the films in ascending order of degree for each of the features indicative of degeneration in the proximal and distal interphalangeal joints of digit V — narrowing of joint spaces, flattening of articular surfaces of middle phalanx, and angularity of the margins of those surfaces.

All 6 assessments (3 at the proximal and 3 at the distal joint) were done independently of each other, so far as the assessor could insure independence. The number of distinguishable ranks or classes in the 6 assessments varied from 5 to 7, and the score for each film in any one assessment was found by dividing its rank by the total number of ranks in that assessment. The 6 scores for each film were then averaged to give an "index of articular degeneration," which, in the 12 films, ranged from 0.36 to 0.84 (i.e., from 36 per cent to 84 per cent of the possible score).

The following correlation coefficients were then calculated: Bone density and age, $-0.573$ ($P = 0.10-0.05$). Bone density and index of articular degeneration, $-0.705$ ($P = 0.02-0.01$). Index of degeneration and age, $+0.590$ ($P = 0.05-0.02$). Bone density and age, after elimination of index of degeneration, $-0.275$ ($P = 0.4$ approx.). Bone density and index of degeneration, after elimination of age, $-0.554$ ($P = 0.10-0.05$). The possible interpretation of these results will be discussed later. (Soft tissue density was not introduced into these calculations because its correlation with age in this group was so low that it had little effect on the age-bone-density relationship.)

### *Residual Intersubject Variation*

In the 41 men whose right hand was studied, the standard deviations, representing individual variation from the regression of bone density on soft tissue density, were (in mm. aluminum): radius, 0.386; lunate, 0.428; capitate, 0.394; metacarpal, 0.175; phalanx, 0.245; (calcaneus, 0.550). These values differed significantly, P from Bartlett's test (5) being very small; and this would still be true if the radius, in which the density was the average of 3 points, were excluded from the comparison.

The coefficients of variation (SD's as percentages of the sample mean densities) were much alike in all bones except the phalanx: radius, 6.8; lunate, 7.5; capitate, 7.3; metacarpal, 5.3; phalanx, 11.7; (calcaneus, 7.1).

If the sample were large enough to provide a standard for normal bone density, and if, as seemed not unlikely, the distributions were approximately Gaussian, the limits (10th and 90th percentiles) of intersubject variation after correction for soft tissue could be found by applying $\pm$ 1.2816SD (P from both tails = 0.2) to the average bone densities estimated from regression equations of bone density on soft tissue density. These limits or ranges ($\pm$) were: radius, 0.495; lunate, 0.549; capitate, 0.505; metacarpal, 0.224; phalanx, 0.314; (calcaneus, 0.705).

In the phalanx, after correction for soft tissue, age and weight, the residual standard deviation was 0.215 mm., and with this value the 1.2816SD range would be $\pm$0.276 mm.

### *Comparison of Women with Men*

*Mean Densities.* — Among the 12 women, aged 19 to 30, the right hand was x-rayed in 10, and their mean densities (in mm. aluminum) were: radius, 4.925; lunate, 4.849; capitate, 4.491; metacarpal, 2.701; phalanx, 1.975. These were all lower than the corresponding means in the 41 men discussed above. In the calcaneus the sex difference was rendered nonsignificant by covariance adjustment (2) for the greater male soft tissue density; but this adjustment was ineffective for the hand bones except the phalanx; i.e., the other male-female differences remained significant.

*Intersubject Variation.*—The standard deviations, representing individual variation from regression on soft tissue, ranged from 0.128 mm. (metacarpal) to 0.360 mm. (lunate). All were lower than the corresponding deviations in men; but this concurrence is not independent evidence, because all 5 bones were on the same films. The highest male/female variance ratio (in the metacarpal) was far from significant at the 5 per cent level.

*Correlations.*—Correlation analysis was applied as to the data from men, chiefly in the radius and phalanx. Where sex differences seemed to exist, they could be reasonably accounted for by the small size of the female sample. None of the 5 bones suggested a correlation between bone density and age.

## DISCUSSION

The report on the calcaneus (2) discussed most of the problems arising in this series of investigations, but the hand study calls for a few further comments.

*Inter-reading Variation.*—Variation between readings of the same film was satisfactorily low, but it is desirable to consider what it actually represented. The photometer, tested by a standard film before and after each hand film, was very stable throughout the reading period of about 5 weeks, but it was thought that some of the variation might have been due to change in the surface of the protective cellulose envelope through repeated use. Fresh envelopes were started after every fiftieth film, and both the envelope numbers and the sequence of readings were recorded. It was, therefore, possible to determine how many films had previously been read in the same envelope, and hence to find the correlation between (a) the reading difference, $R_1 - R_2$, and (b) the difference in the amount of use of the envelope preceding $R_1$ and preceding $R_2$. The coefficient of correlation was $+0.107$—slight and not significant ($P = 0.3 - 0.2$).

The major cause of inter-reading variation was, therefore, presumably the fact that density was not measured on exactly the same 1/16 in. of bone shadow on the two occasions. If so, the variation must represent heterogeneity of bone shadow texture, and it could be reduced by taking the average of several readings at adjacent points on the same occasion. This seems unnecessary, however, because reading variation was a minor cause of intervisit and intersubject differences.

*Sex Differences.*—The sex differences in mean bone densities, persisting after allowance for differences in soft tissue densities, could hardly be attributed to sex differences in size as measured by bone dimensions, stature and weight, because in the male bones, after correction for soft tissue, these variates were not significantly correlated with bone density (except for the weight-density relationship in the phalanx).

Perhaps the cause of the sex difference lies in the different forces to which the hands are subjected in the two sexes. At all events, in establishing norms of bone density, or in the study of aging, male and female hand data should not be pooled, whereas pooling of calcaneus data might be permissible (2).

*Age Differences.*—In the middle phalanx of the little finger there has been discovered a bone with a significant negative correlation between age and x-ray density, and no artifactual explanation of this has, so far, been found adequate. For example, if older men were less able than younger men to place their fingers flat on the film holder, this would presumably cause greater tilt of the phalanx in older men, and hence a higher density reading—the reverse of what was found.

In view of the selection biases in cross-sectional surveys (2) the correlation cannot safely be called an age *change;* but one observation favors that interpretation—the lack of evidence of age correlation in the other 4 wrist and hand bones and in the calcaneus. If the explanation were different hygiene or diet in the different generations represented in the survey, it would seem reasonable to expect a similar influence on all the bones. It is possible, of course, that the x-ray exposure factors were ideal for the phalanx and not for the other (thicker) bones; but, if so, one would expect more evidence of a correlation in the metacarpal than in the carpals and radius, and this was not found.

*Relationship of Bone Density to Degeneration of Joints.*—The "index of articular degeneration," although not the best conceivable device for assessing articular changes, expressed a well-known phenomenon, increasing degeneration with age, by a numerical estimate ($r = +0.590$ in the 12 oldest men) and thus provided a tool to explore the interrelationships

between bone density, joint degeneration, and age.

By elimination of joint degeneration, the age-density relationship was reduced to a value that was far from significant; but one must be cautious in the biologic interpretation of the arithmetic of partial correlation. For example, instead of articular degeneration, the elimination of some other anatomic or physiologic variate, similarly correlated with age, but not otherwise related to bone density, might reduce the age-density correlation to a nonsignificant value. However, even after the elimination of age, there was still a suggestion (although not significant at the 5 per cent level) of a relationship between bone density and the index of articular degeneration.

To suggest that, in order to avoid bias in a gerontologic study of bone density, one must eliminate subjects with signs of articular degeneration, would, in effect, eliminate the study itself. Probably the most useful concept, at present, is that loss of bone density, even in the middle of the phalangeal shaft, is part of an osteo-articular degeneration.

*Further Research.* — The examination of other fingers in the same films might be suggested, but if significant correlations with age were again found, this would not be independent confirmation, and the absence of detectable correlation could lead only to speculations regarding the reasons. It would seem more profitable to pass to a new and larger series of subjects, and to obtain from them, besides postero-anterior films, satisfactory latero-medial films, in order to make a direct adjustment for bone thickness, independent of the soft tissue correction. A more thorough study of the relationship between bone density and articular degeneration is also desirable.

The magnitude of the age relationship discovered here is not great, and for the assessment of normality of bone density in individual subjects it seems, so far, to have little value. However, two points should be noted: (a) The estimates have been based on the assumption of linear regression, and a larger sample might well show a steeper descent in the later decades than in early adult life; (b) Because soft tissue masks mineral changes in bone, it is quite possible that a 5 per cent difference in bone density represents a much greater difference in mineral content. The discovery of an age correlation in a phalanx has provided a starting point for the exploration of such questions.

SUMMARY

In postero-anterior roentgenograms of the hands of 50 symptom-free Canadian white adult males (students, professional and business men aged 20 to 84) and 12 females of the same classes (aged 19 to 30), bone shadow densities, determined by Photovolt densitometer, were expressed as equivalent thickness of an adjacent aluminum wedge. The densities were read in the distal part of the shaft of the radius and at the midpoints of the lunate, capitate, metacarpal V, and middle phalanx of the fifth finger. Corrections for interfilm and intersubject differences in overlying soft tissue density were derived from the linear regression of bone density on adjacent soft tissue density.

Differences between replicate readings of the same films, under highly standardized conditions, contributed only a small part of the variation found between films of the same hands taken on different visits usually 2 to 4 weeks apart.

In 32 men, whose right and left hands were x-rayed, all 5 bones were denser in the right hand, and the difference was significant except in the lunate.

In 41 men who each provided a film of the right hand, the mean densities (in mm. aluminum) varied from 5.689 in the radius to 2.096 in the phalanx. After correction for soft tissue the intersubject standard deviations varied from 0.428 mm. in the lunate to 0.175 mm. in the phalanx, and the coefficients of variation ranged from 11.7 per cent in the phalanx to 5.3 per cent in the metacarpal.

There was no significant correlation between bone densities and linear dimensions of the bones on either the postero-anterior or latero-medial films, or between bone densities and stature in the two bones examined for this purpose (radius and lunate).

The positive correlations between bone density and body weight were rendered nonsignificant, except in the phalanx, by correction for soft tissue density.

After correction for soft tissue the coefficients of correlation between bone density and age in the 41 right hands were low and far from significant in 4 of the bones, but in the phalanx, even after correction for weight as well as soft

tissue, the age correlation was −0.414 (P less than 0.01). The regression, if accepted as linear, would represent an average diminution of about 5 per cent of the mean density of the sample per 20 years of additional life. Confidence limits for this estimate and for the regression coefficients of the other bones are presented.

In the 10 women whose right hands were x-rayed, the mean densities of all 5 bones were lower than in the corresponding bones of the 41 men, and the differences remained significant, except in the phalanx, after adjustment for soft tissue. It did not seem possible to account for it by sex differences in size as measured by bone dimensions, stature, and weight. There was no suggestion of an age-density correlation in the females.

The age relationship discovered in the male phalanx is discussed as a starting point for further research.

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# NEWER CLINICAL AND LABORATORY STUDIES IN THE AGED. XV. CHANGING LIPOPROTEIN PATTERNS IN THE AGED

## A Follow-up Study

A. ALLEN GOLDBLOOM, M.D., HAROLD B. EIBER, M.D., AND ISIDORE DANISHEFSKY, Ph.D.

*(From the Medical Service of New York Medical College—Metropolitan Medical—Center (Bird S. Coler Hospital Division), New York)*

Previous studies from this laboratory (2, 3, 4, 5, 9) carried out on 100 apparently normal individuals aged 80-100 years have failed to reveal any clear-cut correlations between the chemical serum lipid partitions, the $S_f$-lipoproteins as measured by the ultracentrifuge method, and the lipid distribution diagrams (lipidograms) determined by paper electrophoresis. The findings of these investigations indicated the existence of a "threshold age" at approximately 60-75 years, (6, 7) after which there was a decline in the values of total serum lipids, lipoprotein molecules, and Atherogenic Index (A. I.), even in the presence of microscopic atherosclerosis (1).

The purpose of the present investigation was to restudy after three years the lipoprotein patterns of the remaining original apparently normal individuals, age 80-100 years; only 22 subjects were still living in the institution and available for the study.

### MATERIAL AND METHODS

The study included 11 men and 11 women between the ages of 80 and 100 years (average age, 91 years for each sex). Twenty ml. of venous blood were withdrawn from the fasting subjects. The serum lipoprotein molecules of varied classes, $S_f$ 0-12, $S_f$ 12-20, $S_f$ 20-100, $S_f$ 100-400 and $S_f$ 12-400, were determined. The significance of the atherogenic potentialities derived from the $S_f$ lipoprotein values was indicated by the atherogenic index. The details of the methods used have been given in a previous publication (5). The recorded values were compared with those obtained 3 years ago in 1953 (8).

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### RESULTS

#### *$S_f$ Lipoproteins*

The serum lipoprotein values of classes $S_f$ 0-12, $S_f$ 12-20, $S_f$ 20-100, $S_f$ 100-400, and $S_f$ 12-400 expressed in milligrams per cent have been listed in table 1 for both the male and female individuals. The so-called standard classes of serum lipoproteins are the $S_f$ 0-12 and $S_f$ 12-400. The total milligram per cent of lipoproteins of class $S_f$ 12-400 were obtained by adding the values given for classes $S_f$ 12-20, $S_f$ 20-100, and $S_f$ 100-400. In the table the comparative values for each subject, observed in 1953 and 1956, are also recorded, together with the mean values and standard deviations for the groups.

*$S_f$ 0-12 lipoproteins.*—The mean values observed in 1956 for males and females were, respectively, 359 and 409 mg. per cent, showing an increase for both sexes from the 1953 value. The increase was more marked in the case of the women.

*$S_f$ 12-20 lipoproteins*—The mean value for the males was 54, and for the females 67 mg. per cent, indicating an increase for both groups from the 1953 value; a greater rise was observed for the women than for the men.

*$S_f$ 20-100 lipoproteins*—The average values for males and females were, respectively, 109 and 105 mg. per cent, showing approximately the same increase for both sexes when compared with the 1953 values.

*$S_f$ 100-400 lipoproteins*—The mean value found for the males was 24 mg. per cent and for the females, 14 mg. per cent, representing a decrease for both sexes from the values observed in 1953.

*$S_f$ 12-400 lipoproteins*—The average values found for the males and females for this group of lipoproteins were, respectively, 188 and 185 mg. per cent. These concentrations in the case of both sexes indicate a marked increase from the 1953 values.

TABLE 1. COMPARATIVE SERUM $S_f$ LIPOPROTEIN CONCENTRATIONS (MG.%) AND ATHEROGENIC INDEX (UNITS) IN APPARENTLY NORMAL SUBJECTS 80-100 YEARS OF AGE MALES AND FEMALES, AFTER A THREE-YEAR INTERVAL.

| Subject No. | Age | $S_f$ 0-12 (Mg. %) | $S_f$ 12-20 (Mg. %) | $S_f$ 20-100 (Mg. %) | $S_f$ 100-400 (Mg. %) | $S_f$ 12-400 (Mg. %) | Atherogenic Index (Units) |
|---|---|---|---|---|---|---|---|
| **Men, 1956** | | | | | | | |
| 4 | 96 | 372 | 43 | 92 | 2 | 137 | 61 |
| 5 | 86 | 300 | 60 | 79 | 5 | 144 | 55 |
| 9 | 91 | 376 | 50 | 153 | 13 | 216 | 75 |
| 11 | 98 | 319 | 68 | 83 | 0 | 151 | 58 |
| 12 | 96 | 342 | 46 | 58 | 0 | 104 | 52 |
| 13 | 90 | 288 | 32 | 81 | 81 | 194 | 49 |
| 14 | 86 | 539 | 70 | 105 | 25 | 200 | 89 |
| 22 | 99 | 460 | 42 | 107 | 33 | 182 | 78 |
| 17 | 86 | 275 | 30 | 7 | 0 | 37 | 34 |
| 15 | 86 | 248 | 84 | 270 | 55 | 409 | 96 |
| 16 | 85 | 434 | 74 | 169 | 47 | 290 | 94 |
| Mean | | 359 (SD 89) | 54 (SD 18) | 109 (SD 69) | 24 (SD 27) | 188 (SD 97) | 67 (SD 21) |
| **Women, 1956** | | | | | | | |
| 1 | 86 | 497 | 67 | 152 | 27 | 246 | 93 |
| 2 | 94 | 452 | 102 | 182 | 17 | 301 | 98 |
| 3 | 89 | 389 | 106 | 148 | 7 | 261 | 85 |
| 6 | 95 | 433 | 85 | 120 | 14 | 219 | 82 |
| 7 | 89 | 467 | 63 | 87 | 8 | 158 | 74 |
| 8 | 97 | 368 | 43 | 94 | 17 | 154 | 64 |
| 10 | 94 | 317 | 53 | 56 | 0 | 109 | 51 |
| 21 | 93 | 356 | 44 | 17 | 0 | 61 | 46 |
| 19 | 83 | 322 | 39 | 76 | 11 | 126 | 54 |
| 18 | 101 | 479 | 47 | 110 | 34 | 191 | 81 |
| 20 | 90 | 417 | 85 | 109 | 19 | 213 | 79 |
| Mean | | 409 (SD 62) | 67 (SD 24) | 105 (SD 46) | 14 (SD 10) | 185 (SD 72) | 73 (SD 18) |
| **Men, 1953** | | | | | | | |
| 4 | 93 | 407 | 33 | 27 | 12 | 72 | 53 |
| 5 | 83 | 255 | 26 | 34 | 56 | 116 | 46 |
| 9 | 88 | 307 | 48 | 68 | 45 | 161 | 59 |
| 11 | 95 | 323 | 46 | 10 | 7 | 63 | 43 |
| 12 | 93 | 330 | 47 | 40 | 98 | 185 | 50 |
| 13 | 87 | 309 | 32 | 88 | 99 | 219 | 69 |
| 14 | 82 | 444 | 64 | 73 | 140 | 277 | 93 |
| 22 | 96 | 450 | 46 | 41 | 15 | 102 | 63 |
| 17 | 82 | 260 | 20 | 28 | 13 | 61 | 37 |
| 15 | 83 | 298 | 65 | 78 | 83 | 226 | 69 |
| 16 | 82 | 343 | 58 | 78 | 57 | 193 | 68 |
| Mean | | 339 (SD 67) | 44 (SD 15) | 51 (SD 27) | 57 (SD 44) | 152 (SD 74) | 59 (SD 16) |
| **Women, 1953** | | | | | | | |
| 1 | 83 | 379 | 42 | 44 | 59 | 145 | 63 |
| 2 | 90 | 246 | 66 | 111 | 98 | 265 | 71 |
| 3 | 85 | 235 | 49 | 58 | 27 | 134 | 47 |
| 6 | 92 | 262 | 62 | 64 | 54 | 180 | 58 |
| 7 | 86 | 287 | 53 | 42 | 69 | 164 | 74 |
| 8 | 93 | 392 | 25 | 6 | 7 | 38 | 46 |
| 10 | 91 | 378 | 34 | 57 | 19 | 110 | 57 |
| 21 | 90 | 203 | 11 | 0 | 0 | 10 | 22 |
| 19 | 80 | 208 | 15 | 8 | 14 | 37 | 28 |
| 18 | 98 | 431 | 55 | 102 | 32 | 189 | 76 |
| 20 | 82 | 349 | 57 | 54 | 113 | 224 | 74 |
| Mean | | 306 (SD 83) | 43 (SD 19) | 50 (SD 36) | 45 (SD 37) | 136 (SD 81) | 56 (SD 19) |

TABLE 2. COMPARISON OF ARITHMETIC MEAN VALUES OF $S_f$ LIPOPROTEIN MOLECULES (MG.%) AND ATHEROGENIC INDEX (UNITS) OF APPARENTLY NORMAL AGED ADULTS, 80-100 YEARS, COMPARED TO MIDDLE-AGED ADULTS.

| Standard Lipoprotein Level | Males | | | Females | | |
|---|---|---|---|---|---|---|
| | Normal | 80–100 | Difference | Normal | 80–100 | Difference |
| | Average 49 years | Average 91 years | | Average 44 years | Average 91 years | |
| $S_f$ 0- 12 | 361 | 359 | − 2 | 324 | 409 | +85** |
| $S_f$ 12- 20 | 76 | 54 | −22* | 70 | 67 | − 3 |
| $S_f$ 20-100 | 109 | 109 | 0 | 78 | 105 | +27 |
| $S_f$ 100-400 | 21 | 24 | + 3 | 10 | 14 | + 4 |
| $S_f$ 12-400 | 206 | 188 | −18 | 158 | 180 | +27 |
| Atherogenic Index (A. I.) | 74 | 67 | − 7 | 61 | 73 | +12 |

* Statistically significant at 5% level
** Statistically significant at 1% level
} "t-test"

TABLE 3. CHANGES IN PRESENT VALUES OF EACH VARIABLE COMPARED TO VALUES OF THREE YEARS AGO.

| Standard Lipoprotein Level | Males | Females |
|---|---|---|
| $S_f$ 0- 12 | 20 | 103** |
| $S_f$ 12- 20 | 10 | 24* |
| $S_f$ 20-100 | 54* | 55** |
| $S_f$ 100-400 | −33* | −31* |
| $S_f$ 12-400 | 36 | 49 |
| (A. I.) Atherogenic Index | 8 | 17* |

* Statistically significant at 5% level
** Statistically significant at 1% level
} (t-test)

The findings with regard to the serum lipoproteins mentioned above have thus revealed an increase in the concentrations after the three-year interval for all lipoprotein groups, except the $S_f$ 100-400 class.

The difference in the $S_f$ 12-20 lipoprotein concentration in the aged males as compared with the level in normal middle-aged men was found to be statistically significant at the 5 per cent level. In the case of the women the difference between the $S_f$ 0-12 serum concentration in aged subjects and the values observed in middle-aged females was statistically significant at the 1 per cent level (table 2).

### *Atherogenic Index*

The Atherogenic Index, expressed in units, is derived from the following formula:

$$\text{Atherogenic Index (units)} = \frac{1.0\ (\text{Standard } S_f\ 0\text{-}12) + 1.75\ (\text{Standard } S_f\ 12\text{-}400)}{10}$$

It is of interest to note that in the present observations the average Atherogenic Index was found to be markedly higher in both sexes in 1956 as compared with the values obtained in the same individuals in 1953 (table 1).

In the analyses performed in 1956 the old male and female subjects showed average values, respectively, of 67.4 units (SD 21) and 73.4 units (SD 18). The value for the men is lower than the mean value of 74 units observed for middle-aged men, while that for the women is significantly higher (average value for middle-aged women, 61 units) (table 2).

It is of interest to note that with constant conditions prevailing over a three-year period 55 per cent of the subjects had an increased Atherogenic Index, 18% showed decreased values, and 27 per cent remained unchanged (tables 1 and 3). Pathologic (autopsy) specimens showed the presence of microscopic atherosclerosis, with normal lipoprotein values (1).

### *Statistical Analysis*

The statistical evaluation of the observed differences in the concentrations of $S_f$ lipoproteins and in the Atherogenic Index between the 1953 and 1956 analyses was obtained from the t-test as follows:

$$t = \frac{M_1 - M_2}{\sqrt{\frac{1}{N}\left(S_1^2 + S_2^2\right)}}$$

$M_1$ = Mean value (1953)
$M_2$ = Mean value (1956)
$N$ = Number of subjects in each group
$S_1$ = Standard deviation (1953)
$S_2$ = Standard deviation (1956)

The statistical analysis showed the following findings: 1) A significant change in all $S_f$ groups for females; 2) A significant change in the $S_f$ 20-100 and $S_f$ 100-400 groups for males; 3) The change in the $S_f$ 20-100 group to be positive and $S_f$ 100-400 negative; 4) An increase in the Atherogenic Index for females.

SUMMARY

Apparently normal individuals, aged 80-100 years, institutionalized for custodial care rather than medical reasons, were observed after a period of three years. The findings revealed an increase in the serum lipoprotein concentrations after the three-year interval for all lipoprotein groups except the $S_f$ 100-400 class. The lipoprotein values found in the old men were lower than in middle-aged normal males, whereas the serum levels in the old women were higher than in middle-aged normal women. The mean atherogenic index values increased for both sexes during the three-year period. The mean value found for the men was lower and the mean value for the women higher than the average values observed in normal middle-aged adults.

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# LIGHT AVERSION MOTIVATION IN PSYCHOLOGIC STUDIES OF AGING IN RATS

JACK BOTWINICK, Ph.D., EDWARD A. JEROME, Ph.D., JAMES E. BIRREN, Ph.D., AND JOSEPH F. BRINLEY, M.A.

*(From the Section on Aging, Laboratory of Psychology, National Institutes of Mental Health, Public Health Service, U. S. Department of Health, Education and Welfare, Bethesda, Maryland)*

One problem related to studies of learning and other types of performance in animals of different ages is the equivalence of the motivating conditions. It is possible, for example, that three days of food deprivation may have different motivational strength for older and younger rats. There is also the possibility that the rapidity of satiation of the motivating circumstances varies with age. These considerations are important if we want to separate the possible age differences in the capacity to perform from the circumstances of motivation.

To circumvent these problems and the need to manipulate motivating factors such as food and electric shock, the technique of motivation by light aversion was studied for its efficacy in projected aging studies on rat learning. With this technique rats, normally nocturnal animals, can avoid light by crossing a barrier into a dark chamber, darkness or the avoidance of light being the only reward. Animals satiated with food and water can be run in environments similar to laboratory cages.

Motivation by light aversion has other advantages as has been pointed out in a study by Jerome and Flynn (1). The control of hunger drive requires a feeding schedule which if disturbed causes an irregularity in the data. In addition, when food is used as incentive, interpretation is difficult if learning involves many successive trials in a given period. This is so because as the animal is receiving food reward for successful trials, the animal's need for food decreases. It was also indicated in that study (1) that shock motivation may have the undesirable effect of disturbing the emotional equilibrium of the animal. Other studies using light aversion motivation have been concerned with the effects of the intensity of the light (2), the amount of time in the dark (3), and the role of hunger in such a procedure (4).

Because the technique using light aversion does not require any special feeding regimen, and animals may have food and water as they wish, and because it is not likely that motivation by light aversion disturbs the animal in an emotional way, nor is it likely that differential age effects of such motivation would be great, it was decided to test an apparatus involving the use of light aversion as a source of motivation. It was thought that such a test would be a contribution to method in learning studies involving the aging of rats.

## MATERIAL AND METHODS

*Subject*—The subjects of this study were 48 Sprague-Dawley rats, 24 males and 24 females equally divided into groups of approximately 1 and 2 years old. All rats were naive with respect to learning studies and were maintained on an *ad libitum* food and water schedule. Diets were Purina Laboratory Chow with weekly supplements of raw horse meat and fresh fruit and vegetables.

*Procedure.*—Old and younger male rats were run in alternate fashion until all 24 were completed. Following this, the cage was washed and the female rats were run, once again, alternating young and older rats.

Each rat was given three trials in one week. The first lasted a half hour, the first 15 min. of which was considered to serve as a period of adaptation for the rat to the apparatus. Consequently, measurements were taken only of the last 15 min. of this trial. During the second and third trials, which lasted the duration of 15 min. each, no adaptation period was given and measurements were made immediately upon putting the animal in the apparatus.

*Apparatus.*—The apparatus of this study was a metal test cage the inside dimension of which was approximately 19¼ in. long, 12¼ in. wide, and 4 in. high. The floor of the cage was of wire mesh. The cage was divided in

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half in such way that entry between chambers was possible only by way of a single door in the center hinged to the roof so that it could be opened and closed by any minimum pressure that the rat might place on it. There was a space of approximately 1/4 in. between the bottom edge of the door and the floor of the cage.

The center of the cage was balanced on a fulcrum-like bar and the rat's weight caused a slight tilt of the cage. The apparatus was connected to a series of interval timers so that when one chamber of the cage was illuminated, the other was darkened. The rats, to avoid light, would simply have to cross into the darkened chamber by way of the door. When they did so, they would remain in darkness for 15 secs., after which time the chamber lit up and the other chamber was darkened.

Crossings were automatically recorded on an Esterline-Angus recording apparatus, and the position of the rat with respect to light and dark was similarly noted. Two types of measurements were made. One, a *percentage* measurement, was to determine whether, with the advent of light, the animal crossed or did not cross. The other, a *rate* measurement, was the number of crossings made during a stipulated time if the animal did cross.

## RESULTS

The data of this study, i.e., the crossing scores of the animals, are presented in table 1. When these scores are plotted, by trial, in frequency distributions as in figure 1, it is seen that there is skewing in the data. If curves were drawn for those parts of the histograms that exclude non-crossers, 10 would appear to be a reasonable cut-off point for the three trials. It was decided, therefore, to use 10 as a criterion, i.e., rats crossing less than 10 times are not considered to be performing adequately.

*Percentage.*—With 10 as the criterion of acceptability, the number of rats in each group of 12 that crossed at least 10 times into the dark during a 15 min. period, is shown in table 2. When chi square tests were performed with these values* for each of the three trials, no statistically significant differences between age groups were found ($p>.05$).

* When chi square tests were performed with percentage of crossers defined as rats making one or more entries into the dark during a 15-min. trial, the same results were obtained.

TABLE 1. NUMBER OF CROSSINGS OF RATS OF TWO AGE GROUPS OF BOTH SEXES DURING THREE 15-MINUTE TRIALS.

| | 12 Months | | | | | | 24 Months | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Male | | | Female | | | Male | | | Female | | |
| Trial..... | 1* | 2 | 3 | 1* | 2 | 3 | 1* | 2 | 3 | 1* | 2 | 3 |
| | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0† | 0 | 0 | 0 |
| | 2 | 14 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 |
| | 3 | 18 | 29 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | 7 | 21 | 39 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 3 | 0 |
| | 12 | 20 | 26 | 0 | | 0 | 0 | 9 | 11 | 2 | 25 | 28 |
| | 13 | 20 | 12 | 0 | | 0 | 0 | 11 | 16 | 3 | 35 | 30 |
| | 17 | 23 | 30 | 5 | 12 | 17 | 14 | 18 | 6 | 4 | 15 | 12 |
| | 18 | 25 | 25 | 14 | 35 | 40 | 18 | 25 | 32 | 10 | 7 | 12 |
| | 20 | 26 | 21 | 16 | 22 | 26 | 24 | 36 | 38 | 15 | 26 | 41 |
| | 24 | 26 | 24 | 19 | 26 | 34 | 26 | 30 | 33 | 21 | 34 | 32 |
| | 26 | 30 | 30 | 25 | 42 | 29 | 28 | 30 | 32 | 22 | 29 | 28 |
| | 27 | 36 | 38 | 26 | 29 | 27 | 30 | 31 | 26 | 33 | 36 | 40 |

* Rank ordered for first trial.

† This rat made no crossings during the first two trials and was not run for a third trial. Subsequently, all rats were run for three trials regardless of the number of crossings.

Although table 2 shows there is an apparent sex difference in the younger age group, the statistical tests did not indicate this in the present sample. The same is true for differences between the three trials.

*Rate.*—Considering only acceptable animals, i.e., those making 10 or more crossings, it may be asked whether young rats make more crossings than old ones. Also, it may be asked whether the obtained result is related to the sex of rats. For trials, 1, 2, and 3 standard t-tests

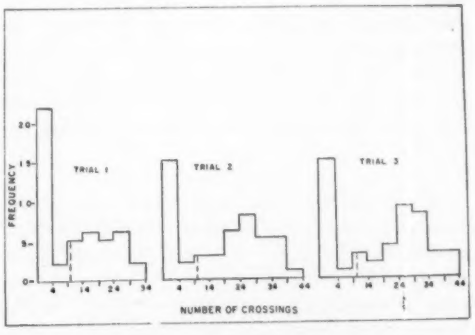


Fig. 1. Distribution of numbers of crossings in three successive 15-minute trials of all groups combined. N=48 rats; males and females equally divided into age groups of approximately 12 and 24 months. Vertical dashed lines indicate that 10 was chosen as the criterion of accepting rats as "crossers."

TABLE 2. NUMBER OF RATS, IN EACH GROUP OF 12 MAKING 10 OR MORE CROSSINGS DURING SUCCESSIVE 15-MINUTE TRIALS.

| Age | 12 Months | | | 24 Months | | |
|---|---|---|---|---|---|---|
| Trials | 1 | 2 | 3 | 1 | 2 | 3 |
| Male | 8 | 11 | 10 | 6 | 7* | 7 |
| Female | 5 | 6 | 7 | 5 | 7 | 8 |
| Total | 13 | 17 | 17 | 11 | 14 | 15 |

* One rat made no crossings during the first two trials and was not run for a third trial. Subsequently, all rats were run for three trials regardless of the number of crossings.

were made utilizing the crossing scores of only the acceptable animals. The results indicate no significant differences between age or sex groups ($p>.05$).

Another type of analysis of the rate measurements is one described by Mood (5). For trials 1, 2, and 3, chi square tests were separately made to analyze age and sex differences and their interactions by comparing the number of rats in each of the 4 groups whose crossing scores were above or below the median of the combined groups that were tested. Again, no reliable differences were found.

Although the data of each of the three trials were analyzed, it is the third trial that is considered the most important. It is in this trial that the rats had the most experience with the procedure, and it is from this trial that the most accurate predictions might be made. It is possible to consider the first trial as one of adaptation since it immediately followed the 15-min. trial in the darkened test cage and was the first experience the rats had with the light. It may be observed from tables 1 and 2 that it is in the third trial where there is greatest apparent similarity between the 4 subgroups.

## DISCUSSION

The purpose of this study was to answer the general question of whether the technique of motivation by light aversion is suitable for aging studies of rat learning. Although the concept of suitability is necessarily vague, certain important practical and theoretic considerations are included under it. For example, in this study where little or no learning was required from the rats, there were no reliable age differences in the relevant behavior, i.e., crossings. Thus, it would be straightforward to analyze for age differences in learning ability when the problem is changed to require more learning from the rat.

To answer the general question as to whether the technique is suitable for aging studies of rat learning, there are two considerations. One is whether it is suitable for all Sprague-Dawley rats, and the other is whether it is suitable for a sample of rats that cross. With respect to the first consideration, the conclusion drawn from these data is that one may work with a representative sample as far as age is concerned. There is the possibility, however, that it is necessary to control for sex since the younger females may not run as well as other groups. With respect to whether the technique is suitable for aging studies on rats that do cross, the data indicate that it is, regardless of sex of rats.

If, in this study, significant age differences in percentage and rate of crossing had been found, then the results of studies with more complex learning problems would require statistical or other kinds of adjustments because of the different base lines for the age groups. Regardless of how ingenious the adjustments might be, interpretation would be dependent upon them rather than upon the direct outcome of the observations.

The results of this study suggest that no adjustments would be required. This and the desirable features of motivation by light aversion previously mentioned make the technique a promising one for learning studies on rat aging.

## SUMMARY

In order to evaluate the suitability of a technique for learning studies on rat aging utilizing light aversion as motivation, experiments were carried out on two groups of Sprague-Dawley rats of approximately 1 and 2 years of age. A special cage was used, one chamber of which was illuminated and the other darkened; the crossings of the animals were recorded automatically.

It was found that age groups were statistically similar with respect to percentage of animals that cross, rate of crossings, number of rats that are crossers by a criterion of acceptability, and rate of crossings of the acceptable rats.

It was concluded that the method of motivation by light aversion is suitable for age comparisons in rat learning, at least within the age period of one or two years.

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# SET IN RELATION TO AGE*

JACK BOTWINICK, Ph.D., JOSEPH F. BRINLEY, M.A., AND JAMES E. BIRREN, Ph.D.
*(From the Section on Aging, Laboratory of Psychology, National Institute of Mental Health, National Institutes of Health, Public Health Service, U. S. Department of Health, Education and Welfare, Bethesda, Maryland)*

An attempt to determine the locus of the increased reaction time with age has been made in a recent study (1). Indicated in that study were the possible contributions that processes within the central nervous system might make to the loss of speed with advancing years. If, as some writers believe (e.g., 7), set is a central phenomenon, then we may expect an age change in the role of set in the slowing process.

The term "set" refers to the development or maintenance of an expectancy. Both long-term and short-term expectancies or anticipations are often included in the concept of set although the same mechanisms may not be involved (3). In the present study set refers to expectancies to respond within short time intervals of a few seconds. Specifically set is defined in the present study by the relationship between the speed of response and the preparatory interval in a reaction time experiment. The preparatory interval is the time between an initial "ready" or warning signal and a succeeding stimulus calling for a response.

In an excellent review of the literature on the concept of set, Gibson (4) categorized 4 major kinds of results relating to the preparatory interval. First, Breitwieser (2), Woodrow (9, 10), Woodworth (11) and others concluded that reaction time is a function of the preparatory interval such that optimum reaction occurs with a preparatory interval of about 2 to 3 sec., and slower reaction times occur at intervals longer and shorter than this. Second, preparatory intervals of uniform length are favorable to reaction time, but with many repetitions, the speed of reaction will be almost instantaneous. Third, Woodrow (9, 10) showed that intervals varied irregularly make for slower reaction times than do intervals varied in regular sequence. Fourth, Mowrer (7) demonstrated that the greater the time difference between an interval and a preceding interval regularly presented, the greater will be the reaction time.

Some of these concepts have been applied, with success, in studies with schizophrenic patients (5, 8). These studies showed that it is useful to distinguish schizophrenics from control subjects by certain characteristics of the set phenomenon.

The present study has as its purpose to investigate age changes in an aspect of set or expectancy. More specifically, this study relates age changes in reaction time as a function of an irregular series of preparatory intervals.

## METHOD

*Subjects.*—There were 54 white male subjects: 27 aged 20 to 36 years, and 27 aged 61 to 83 years. The younger group comprised 23 persons who were full-time employees of the Public Health Service and 4 individuals who were religious research volunteers. The older group comprised 18 individuals who were full-time employees of the Public Health Service, 5 individuals who were retired community residents, and 4 individuals who were retired but residing in a religious home for the aged. The mean age of the younger group was 27.0 years, $\sigma=4.5$, and the mean age of the older group was 68.0 years, $\sigma=6.8$.

*Procedure.*—Each subject was given instruction trials preceding two series of simple finger reaction time measurements to an auditory stimulus. Both series consisted of 25 measurements each and will be referred to as series 1 and 2. There were 8 preparatory intervals used in fixed quasi-random order. The intervals used were of 1.0, 1.5, 2.0, 2.5, 3.0, 4.0, 5.0, and 6.0 sec. duration. Each series contained 4 of the 2.0 sec. intervals, and 3 each of the other 7 intervals. The order of the preparatory intervals were reversed in series 1 and 2.

In between series 1 and 2, 100 reaction time measurements were made for the foot and jaw. This was done for the purposes of another study by Birren and Botwinick (1). As indi-

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* Grateful acknowledgment is due Mr. Samuel Greenhouse for his valuable advice on the statistical analyses.

cated in that study, the correlation between reaction times of series 1 and 2 was 0.92.

Each subject was instructed to press a microswitch, used as a response key, when given a verbal instruction, "ready," and when simultaneously presented with a warning signal. This warning signal was a glow of neon bulb presented for 0.50 sec.

The subject was further instructed to release the response key as soon as possible after hearing a tone stimulus. The stimulus was presented by ear phones for 0.20 sec. duration. Its frequency was 1000 cycles per sec., and its intensity was approximately 85 db.

The reaction, the release of the response key, required a minimum finger movement which broke a circuit to a standard electric timer. Response time was read to the nearest 0.01 sec. Hunter interval timers were used to control the durations of the warning signal, preparatory interval, and the tone stimulus.

## RESULTS

For each subject, median reaction times were computed for each preparatory interval of both series 1 and 2. Medians were used rather than means because of the skewing that occurs with latency measurements. The means of these median reaction times of series 1 and 2 of each subject for each preparatory interval are shown in table 1 along with the respective $\sigma$s.

Analyses of variance were run with the medians to determine the significance of age differences with respect to the relationship between reaction time and preparatory interval. Major interest in the analyses of variance was the F-tests associated with the 8 preparatory intervals, the two age groups, and the interaction between age levels and the preparatory intervals. These and other variances are shown in table 2.

The differences between the 8 preparatory intervals are statistically significant ($p<.01$). This is so when the results are analyzed from the data of the combined age groups (table 2), from the data of the older group alone (table 3), and the younger group alone (table 4). Since there is a trend to the relationships, shown in figure 1, these significant F-ratios are taken as additional evidence confirming the findings of previous investigators describing reaction time as a function of the preparatory interval.

TABLE 1. SIMPLE AUDITORY REACTION TIME AS A FUNCTION OF THE PREPARATORY INTERVAL IN YOUNG AND ELDERLY SUBJECTS.

| | | Preparatory Interval in Seconds | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | 1.0 | 1.5 | 2.0 | 2.5 | 3.0 | 4.0 | 5.0 | 6.0 |
| Young 20-36 years N=27 | Mean* | 220 | 201 | 186 | 182 | 177 | 176 | 176 | 179 |
| | $\sigma$ | 50 | 52 | 34 | 40 | 42 | 36 | 39 | 34 |
| Elderly 61-83 years N=27 | Mean* | 311 | 263 | 246 | 240 | 225 | 213 | 222 | 223 |
| | $\sigma$ | 94 | 79 | 64 | 72 | 65 | 58 | 64 | 58 |
| Elderly–Young | Mean* diff. | 91 | 62 | 60 | 58 | 48 | 37 | 46 | 44 |

* Mean of the individual median measurements, in msec.

TABLE 2. SUMMARY OF ANALYSIS OF VARIANCE FOR BOTH AGE GROUPS COMBINED.

| Source of Variation | d.f. | Means Sq. (10000) | Error* | F |
|---|---|---|---|---|
| Preparatory interval (P) | 7 | 607 | I × P | 50.88† |
| Age (A) | 1 | 6761 | I | 19.94† |
| Series (S) | 1 | 3 | I × S | .05 |
| Age × Preparatory interval | 7 | 77 | I × P | 6.42† |
| Age × Series | 1 | 4 | I × S | .07 |
| Preparatory interval × Series | 7 | 31 | P × S × I | 3.44† |
| Age × Series × Preparatory interval | 7 | 5 | | |
| Total | 31‡ | 381 | | |

* Error terms obtained by pooling appropriate mean squares from tables 3 and 4. In each case, the corresponding mean squares differed significantly. This, of course, made the F-tests approximate tests of significance which we attempted to correct by using as the degrees of freedom for error only the degrees of freedom associated with one of the mean squares and not the sum of the degrees of freedom in the two groups.

† Significant at $p < .01$. Other F-ratios are not significant.

‡ This total does not reflect all the degrees of freedom associated with the within age group sources of variation.

TABLE 3. SUMMARY OF ANALYSIS OF VARIANCE FOR OLDER GROUP.

| Source of variation | d.f. | Means Sq. (10000) | Error | F |
|---|---|---|---|---|
| Preparatory interval (P) | 7 | 551 | I × P | 29.00* |
| Series (S) | 1 | 7 | I × S | .08 |
| Individual (I) | 26 | 486 | | |
| Individual Preparatory interval | 182 | 19 | P × S × I | 1.19 |
| Individual × Series | 26 | 84 | P × S × I | 5.25* |
| Preparatory interval × Series | 7 | 29 | P × S × I | 1.81 |
| Preparatory interval × Series × Individual | 182 | 16 | | |
| Total | 431 | 58 | | |

* Significant at $p < .01$. Other F-ratios are not significant.

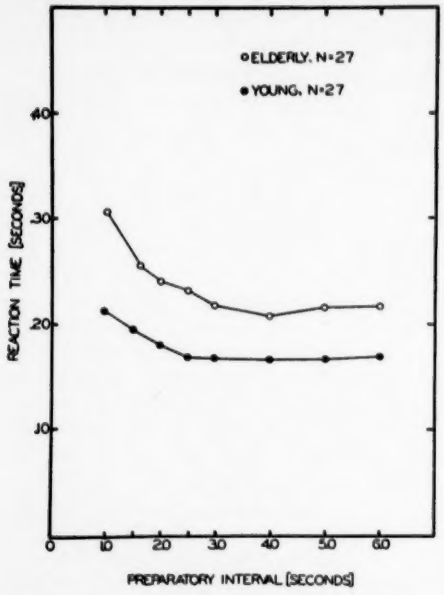


Fig. 1. Age differences in the relationship between mean reaction time and preparatory interval. The mean reaction time is based on median values of individual subjects. Age of elderly and young subjects were 61 to 83 years and 20 to 36 years, respectively. The curves are statistically different in shape.

Of greater interest to this study, however, is the age difference in the rate of decline of reaction time with increased length of preparatory interval. The F-test that indicates whether the two functions shown in figure 1 are of the same shape as the ratio of the interaction variance, age × preparatory interval (table 2), or to the interaction variance, individual × preparatory interval within the two age groups pooled (tables 3 and 4). This ratio indicates that the two functions shown in figure 1 are statistically different in shape ($p<.01$). It is concluded, therefore, that there is a significant age effect with respect to the preparatory intervals.

In table 2 it is seen that for general speed of response there is a statistically significant age difference ($p<.01$). In addition to age and preparatory interval, there is the main effect of series. There were no significant differences between series 1 and series 2. This was true for both age groups combined (table 2), for the older group alone (table 3), and for the younger group alone (table 4). The conclusion drawn was that there was no effect attributable to the 100 reaction time measurements intervening between series 1 and series 2 and that there was no change creditable to the course of the second series itself as compared to the first series.

The interpretation regarding the interaction variances involving series is difficult to make. For each age group alone (tables 3 and 4), the interaction variance of series and individuals is statistically significant ($p<.01$), but the age × series interaction (table 1), is not at all significant ($p>.05$). It would perhaps be best not to attribute importance to the statistically significant F-tests involving individual × series because of the small error terms that were used, i.e., the second order interaction. This is particularly true for the younger group (see table 4). These small error terms also entered into the F-tests involving preparatory interval × series. The importance of these F-tests, might, therefore, also be questioned. The preparatory interval × series variance is significant for the younger group and for both groups combined ($p<.01$) but not for the older group.

In considering the interaction variance of individual × preparatory interval (tables 3 and 4), there is statistical significance ($p<.01$) in the younger group, but not ($p>.05$) in the older group. These results are also difficult to interpret because, as before, the error terms that were used, i.e., the second order interactions, are very small.

Each of the variances for the older group table 3) was compared with those of the

TABLE 4. SUMMARY OF ANALYSIS OF VARIANCE FOR YOUNGER GROUP.

| Source of Variation | d.f. | Means Sq. (10000) | Error | F |
|---|---|---|---|---|
| Preparatory interval (P). | 7 | 133 | I × P | 26.60* |
| Series (S)..... | 1 | 0 | I × S | .00 |
| Individual (I)..... | 26 | 192 | | |
| Individual × Preparatory interval..... | 182 | 5 | P × S × I | 2.50* |
| Individual × Series..... | 26 | 35 | P × S × I | 17.50* |
| Preparatory interval × Series..... | 7 | 11 | P × S × I | 5.50* |
| Preparatory interval × Series × Individual... | 182 | 2 | | |
| Total..... | 431 | 19 | | |

* Significant at $p < .01$. Other F-ratios are not significant.

younger group (table 4). In all instances, the variances were numerically larger in the older group, and statistically larger ($p<.05$ to $<.01$) in each instance except series and series × preparatory interval.

## DISCUSSION

The major finding of this study is that the decrease in reaction time as a function of the increase in the length of preparatory interval is significantly different between age groups. Referring to the age differences in reaction time as a function of the preparatory interval in table 1, and to the functions shown in figure 1, it is seen that the largest age difference is with the shortest preparatory interval, i.e., 1 sec. The age differences with the longer intervals are less but appear to be functionally related to the length of the preparatory interval. It is possible, however, that the age difference in reaction time associated with the 1 sec. interval is responsible for the significant interaction age × preparatory interval that was found in this study. In any case, it is clearly indicated that the older group, compared with the younger one, was at a disadvantage with the shorter or shortest preparatory intervals. Two hypotheses may be suggested to explain this result.

One hypothesis is that with age there is an increase in the amount of time required to organize a response or to develop a state of optimum expectancy. The other hypothesis emphasizes the role played by the longer intervals in the series.

This second hypothesis assumes that the irregular preparatory intervals have similar effects on both age groups such that the average expectancy of when the stimulus is to occur is longer than the shortest preparatory interval. Thus the expectancy is one of over-estimation of the time duration of the shortest intervals. This assumption seems to be reasonable in the light of Mowrer's data (7).

The second hypothesis, then, is that the larger age differences with the shorter intervals are explainable by the time required to recover from, or to reorganize as a result of, the over-estimation. Operationally, the difference between the two hypotheses is an emphasis in the first case on the effects of the preparatory interval and an emphasis in the second case on the effects of the interval in relation to the others in the series.

There is tentative evidence for accepting the second hypothesis. Both Woodrow (9) and Klemmer (6) have reported that the speed of a given response is related not only to its preparatory interval, but is also influenced by the preparatory interval of the preceding response. If in a sequence a long preparatory interval precedes a short one, then the reaction time after the short interval is increased; the reverse is true when a shorter preparatory interval precedes a longer one.

Accordingly, the reaction times obtained in the present study were plotted as a function of the difference between the particular preparatory interval and the preparatory interval immediately preceding. As plotted in figure 2, a difference was considered positive if a longer interval preceded a shorter one, and negative if a longer interval followed a shorter one. For example, if a 5 sec. preparatory interval preceded a 1 sec. interval, the reaction time to the 1 sec. interval was plotted against a difference of + 4.0 sec. In figure 2, the abscissa reflects a grouping of several differences between adjacent intervals in the series. The grouping was for the purpose of increasing the reliability of the values.

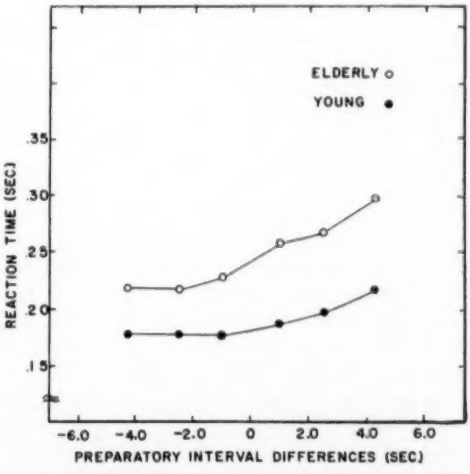


Fig. 2. Age differences in the relationship between mean reaction time and differences in adjacent preparatory intervals in a series. The mean reaction time is based on median value of individual subjects. The abscissa represents a pooling of three adjacent interval differences. The curves are statistically different in shape.

With these grouped data, an analysis of variance showed an interaction of age with differences between preparatory intervals significant at the $p<.01$ level. This indicates a significant difference in the shape of the two curves in figure 2. Such an age difference stands as tentative evidence for the second hypothesis because of the role of the preceding interval, i.e., the inferred role of an overestimated time expectancy.

This evidence is considered only tentative because there is confounding in the data of the effects of the preparatory intervals and the differences between them. With the order of the preparatory intervals employed in this study, the largest positive differences always preceded short preparatory intervals; the reverse was true for largest negative differences. There was less confounding for the smallest differences between the intervals.

Another type of test of the two hypotheses is to measure reaction times for two age groups with both a series of irregular preparatory intervals and of regular preparatory intervals. For the first hypothesis to be tenable, the largest age differences have to be manifested with the shortest intervals in both the regular and irregular series. This is so because the first hypothesis states that more time is required by the elderly than the young to develop an expectancy or to organize for the reponse. This hypothesis, however, may be untenable on the basis that it demands that the time taken up by these processes approach and perhaps exceed 1 sec. At the very least, the time taken up is required to be an appreciable percentage of the interval.

On the other hand, for the second hypothesis to be tenable, age differences in reaction time should be a constant for preparatory intervals presented in a regular series. The reason is that recovery or reorganization is not operative because there is no over-estimation due to other prepratory intervals in the series.

Regardless of which hypothesis is more tenable, there is an additional way of analyzing the data. On the basis of increased reaction time with age, one might expect proportional increases of the latencies in other processes. This may be expected whether the processes involve time required to organize responses or develop expectancies, or whether they involve time required to recover and reorganize from overestimated expectancies. The implication of this explanation is that the finding of the largest age differences with the shortest intervals is a reflection of a basic slowing process with age, rather than a reflection of an additional slowing of other processes.

## SUMMARY

Set was studied as a function of age by comparing two age groups with respect to the relationship between reaction time and an irregularly presented series of preparatory intervals. One age group comprised 27 subjects aged 20 to 36 years, and the other age group comprised 27 subjects aged 61 to 83 years.

Auditory reaction times were measured for each subject by presenting a 1000 cycle, 85 db tone through earphones for 0.20 sec. The subject responded by lifting the finger from a micro-switch. The subject was prepared for the auditory stimulus by a visual warning signal of 0.50 sec. duration. The time between the warning signal and auditory stimulus—the preparatory interval—was varied in 8 time durations, 1.0, 1.5, 2.0, 2.5, 3.0, 4.0, 5.0 and 6.0 secs.

It was found that the largest age differences in reaction time were with the shortest preparatory intervals. This finding, however, may have been due to the fact that the largest age differences in reaction time also occurred when a long interval preceded a short one.

The hypotheses that were suggested, therefore, were either that the elderly group required more time for preparation, or that they required more time to overcome the effects of an overestimated interval of time. A test of these two hypotheses was suggested.

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# IONIZING RADIATION AND THE AGING PROCESS

## A Review

A. C. UPTON, M.D.

*(From the Biology Division, Oak Ridge National Laboratory,* Oak Ridge, Tennessee)*

The growing number of people surviving into old age and the resulting magnification of the problems of gerontology make it increasingly important that means be found to elucidate the mechanisms of aging. In the experimental approach to this question, methods for accelerating or retarding senescence in laboratory animals have long been sought as a possible means of studying the basic factors underlying the aging process.

Although it has been repeatedly confirmed in the last decade that senescence may be greatly delayed in rats (45) as in many other organisms (38) by underfeeding, too little attention has been given to this discovery and to the equally significant observation that animals exposed to ionizing radiation die prematurely from a process resembling accelerated aging (30, 54).

This report surveys existing data on the effects of radiation on the life span. It is hoped that a greater awareness of this information will serve to stimulate further research on the life-shortening action of radiation and may thus contribute to a better understanding not only of radiation injury but of the aging process.

### SURVIVAL TIME VERSUS DOSE OF RADIATION

In general, at a given dose rate the survival time is inversely related to the amount of radiation absorbed. Although death may ensue within minutes, days, or weeks after massive doses of radiation (17), the injuries causing early mortality are largely reparable (6, 48). Hence, if survival extends beyond 30-90 days after exposure, the death rate decreases temporarily to normal, only to rise again after an interval that varies inversely with the dose (fig. 1).

The delayed mortality that occurs months or years after irradiation results from the induction of neoplasms and degenerative changes, which collectively simulate the picture of spontaneous senescence. For example, mice exposed to ionizing radiation from an experimental nuclear detonation (27) exhibited reduction of the life span in proportion to the dose, the shapes of the mortality curves of the irradiated groups being essentially identical to those of the controls (fig. 2). It has been emphasized by others (10 and 58) that the life tables of these irradiated populations are described by the same type of Gompertz function as those of the nonirradiated controls and that senescence was therefore of essentially the same character in both groups and merely accelerated in the irradiated animals in proportion to the amount of radiation received.

If radiation is absorbed over a long period of time, instead of instantaneously, there is, in general, less reduction of longevity per given total dose (6). Mice exposed for the duration of life exhibit shortening of the life span in proportion to the rate at which the radiation is administered (fig. 3). This type of response also occurs in other species of mammals (6, 57). That man behaves similarly is strongly suggested by the data of Warren (65), who noted that radiologists, occupationally exposed to low doses of radiation, die 5-10 years younger than nonexposed men in the general population. Attempts to integrate the experimental and clinical data on life shortening and to predict quantitatively the effects of a given dose on the length of life in man have been reviewed by Berlin and DiMaggio (5).

Although from the foregoing it is evident that large amounts of radiation are not required to shorten life, experimental results obtained with very low doses are equivocal. Mice exposed throughout life to 0.1 r per day of gamma rays exhibited a slightly longer mean survival time than the nonirradiated controls despite a significantly higher incidence of certain neoplasms (41, 44); however, as pointed out by Sacher (58), the longer mean survival resulted from a reduced rate of mortality early in life and does not reflect an increase in the life span, since the death rate of the irradiated animals actually exceeded that of the controls in old age. Similarly, whereas mice exposed early in life to a single dose of 30 rad of X-rays uni-

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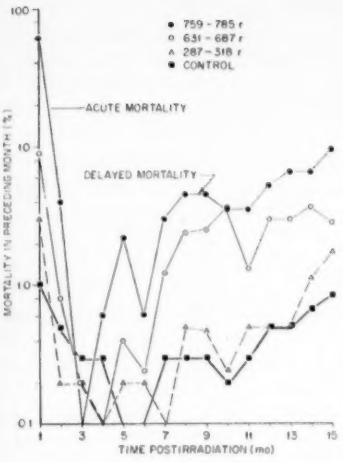


Fig. 1. Time sequence of *acute* (30-day) and *delayed* radiation death in mice exposed instantaneously to gamma rays from an experimental nuclear detonation. Each sample contained at least 220 mice of each sex. The mortality within the first 3 months denotes *acute* radiation death and that occurring later *delayed* radiation death. ●, 759-785 r; ○, 631-687 r; △, 287-318 r; ■, control. (From data of Furth and associates, ref. 27.)

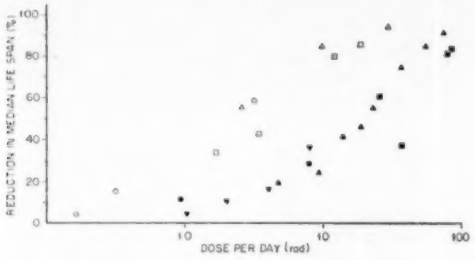


Fig. 3. Shortening of the life span in mice by daily irradiation. Solid symbols denote results of exposure to x-rays or gamma rays. Open symbols denote results of exposure to neutrons. Doses in n units or roentgens were arbitrarily converted to rad by the formulas:

1 n = 2.3 rad, and 1 r = 0.93 rad.

▲, data of Henshaw (30) (X-rays);

△,●, data of Henshaw *et al.* (31) (fission neutrons, tantalum gamma rays);

▼, data of Lorenz (41) (radium gamma rays);

○, data of Evans (20) (cyclotron fast neutrons);

□,■, unpublished data of A. C. Upton and J. A. Sproul (1957) (Po-Be fast neutrons, $Co^{60}$ gamma rays).

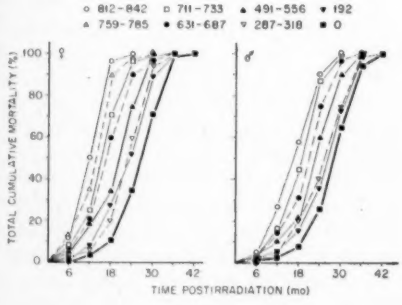


Fig. 2. Effects of varying doses of radiation on the life span. The data denote the survival of mice of the $LAF_1$ strain exposed instantaneously to gamma rays at 6-12 weeks of age and do not include mortality within the first 30 days after irradiation. ○, 812-842 r; △, 759-785 r; □, 711-733 r; ●, 631-687 r; ▲, 491-556 r; ▽, 287-318 r; ▼, 192 r; ■, Control (0 r). (From Furth and associates, ref. 27.)

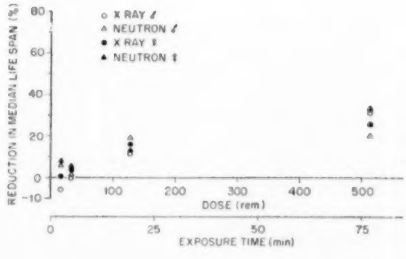


Fig. 4. The median survival of mice exposed early in life to a small amount of X-rays or thermal column radiations (thermal neutrons plus contaminating gamma rays). The mice were of the RF strain and were exposed at 6-8 weeks of age. The doses are expressed in rem (roentgen-equivalent-mammal) on the basis of 30-day lethality. ○. X-ray-exposed males; △, neutron-exposed males; ●, X-ray-exposed females; ▲, neutron-exposed females. (From data of Upton and associates, ref. 64.)

formly exhibited reduction in the life span, those exposed to 15 rad varied in response (fig. 4). Hence, it is not yet certain whether there is a threshold dose or intensity of radiation below which no reduction of the life span is produced.

In any event, proper assessment of the effects of irradiation on longevity should take into account the entire life span, or life table, and not merely the mean length of life of any given population. Furthermore, it is important that the pathologic changes occurring in the irradiated individuals be accurately determined for comparison with those in the controls, since the morbidity and mode of death are of greater physiologic significance than the age at which death occurs.

## MECHANISMS OF DELAYED RADIATION DEATH

Although a detailed comparison of natural and radiation-induced senescence is yet to be made, mice dying prematurely as a result of irradiation are thought to exhibit ostensibly the same pattern of physiologic and pathologic changes as those dying spontaneously. Certain differences are already evident, however, in that the incidence of neoplasms is increased after irradiation, as is the frequency and severity of specific types of non-neoplastic degenerative changes. Salient data on the induction of these diseases by irradiation will be summarized.

## RADIATION-INDUCED LEUKEMIA

The rate of induction of leukemia in mice varies not only with the dose but with the genetic constitution of the strain exposed, age at irradiation, sex, dose rate of irradiation, hematologic type of leukemia induced, and other influences. The available evidence suggests that these factors also play a role in conditioning the susceptibility of human beings to this disease (63). In a large group of patients given radiotherapy for spondylitis, the reported incidence of leukemia seemed to be essentially linear with the dose to the spine, the leukemia rate-doubling dose being less than 100 r (16). Similarly, in the Japanese atomic bomb survivors, an increase of more than one hundredfold in the incidence of leukemia has been observed thus far at sublethal radiation levels (50). Even exposure of the fetus *in utero* to diagnostic radiography may significantly increase the risk of developing leukemia later in childhood (60), as does irradiation of the mediastinum in infancy (59).

The mechanism of the induction of leukemia by irradiation is unknown. In mice, lymphomas may be produced in nonirradiated thymus tissue on implantation into irradiated thymectomized recipients (36, 39). In this instance the radiation apparently acts indirectly through the host, since the grafted thymus is not itself irradiated. Similarly, the induction of myeloid (62) as well as lymphoid (35, 43) leukemia in mice has been found to be greatly inhibited if the volume of hemopoietic tissue irradiated is reduced only slightly by partial shielding. Lymphoma induction has also been inhibited by implantation of viable nonirradiated hemopoietic cells into the irradiated mice (14, 37, 42). Although these experiments suggest that under certain conditions the induction of leukemia by radiation involves indirect factors primarily, rather than a direct cancerogenic action of radiation on hemopoietic tissue, the latter mechanism cannot be excluded in all instances.

## OTHER RADIATION-INDUCED NEOPLASMS

A wide variety of radiation-induced tumors have been reported in man, and neoplasms of virtually all types of tissue may be induced in susceptible animals by large amounts of localized radiation (9, 24, 26). On the other hand, only those tumors that are most readily induced may be caused by whole-body irradiation, since only relatively small amounts of whole-body radiation may be administered without producing early death. If survival is enhanced through such measures as parabiosis, however, larger total-body doses may be applied and additional types of neoplasms thereby induced (7, 21).

The mechanism of tumor induction varies with the type of neoplasm and conditions of irradiation. Some growths seem to be initiated through indirect mechanisms. For example, the induction of ovarian tumors, which occur in a large proportion of female mice sterilized by irradiation, may be inhibited by the shielding of one ovary or by the administration of estrogen (28). This neoplasm, like those arising in intrasplenic ovarian grafts, probably results primarily from hypersecretion of pituitary gonadotropin and not from radiation injury of the ovary per se (23).

Similarly, the thyrotropin-secreting adenomas of the pituitary that are induced in mice by radioactive $I^{131}$ may also be caused by

surgical thyroidectomy or by the administration of antithyroid drugs; hence it is inferred that these neoplasms are induced by hypothyroidism and not by radiation itself (18). On the other hand, whole-body irradiation is believed to exert a cocarcinogenic action in the induction of these pituitary growths under certain conditions (19).

In contrast to leukemia and neoplasms of endocrine organs, the induction of which is mediated through or conditioned by hormonal mechanisms, certain other types of tumors are apparently initiated by the local cancerogenic effects of radiation. Thus localized irradiation may induce the formation of cancer in the skin, lung, fibrous tissue, liver, and other organs (24, 26). Similarly, osteogenic sarcoma may be produced by the irradiation of bone, either from external radiation sources (26) or from isotopes deposited in the skeleton (22, 25).

The period between irradiation and the earliest detectable neoplastic change is relatively long, and the preneoplastic changes taking place in this interval are largely unknown. In certain instances, neoplasia is preceded by local necrosis, inflammation, and regenerative hyperplasia (i.e., radiation dermatitis, osteitis); whereas in other cases such antecedent changes are minimal or lacking (i.e., adenoma of the Harderian gland, lung, breast). The earliest induced leukemias have been observed 2-3 months after irradiation in mice (37) and 2 years after irradiation in man (50). In general, however, the latent period is much longer, i.e., 12 months or more in mice, 5-30 years in man (9, 24). Experimental data indicate that radiation-induced neoplasms tend to occur earlier in life, in proportion to the dose of radiation received, than the spontaneous tumors of corresponding histogenesis.

Because of the high mutagenicity of ionizing radiations, it is tempting to ascribe the induction of neoplasia to radiation-induced somatic mutations (51, 52). The somatic mutation theory of cancerogenesis is not established (11), however, and in the experimental production of lymphomas, neoplasia may conceivably be initiated indirectly in nonirradiated cells, as already cited (36, 39). Hence, in this instance at least, the tumorigenic action of radiation may not be mutagenic in the customary sense.

## RADIATION-INDUCED DEGENERATIVE DISEASES

The most notable examples of specific radiation-induced degenerative diseases are nephrosclerosis, anemia, dermatitis, osteitis, sterility, and cataract. The production of these effects entails widely differing dosages of radiation and involves a variety of different cell types. In general, however, the changes seem to reflect the killing of radiosensitive cells and the harmful action of radiation on blood vessels. The essential features of these diseases will be characterized briefly to indicate their relation to the problem of senescence, since it is evident that the life-shortening action of radiation is attributable to these particular diseases in only a relatively few instances and that it must therefore depend primarily on other effects as yet unknown. Furthermore, whereas some of these diseases simulate changes associated with natural aging, others bear little if any resemblance to the effects of spontaneous senescence.

*Nephrosclerosis.* — Although nephrosclerosis has been recognized for many years as a complication of overexposure of the kidney region to radiation (26), only recently has it been observed in rats (4) and mice (27) surviving whole-body irradiation. The disease develops within months after exposure and may culminate in hypertension and renal failure. The histologic changes include hyalinization of the glomeruli and atrophy of the tubules of the kidneys, associated with inflammation of arteries and arterioles in distant organs. The pathogenesis of the lesion is unknown, but similar changes may be produced in rats by injection of polonium (12). The location of the initial morphologic changes in the glomerulus suggests that the capillary tuft is the site of primary injury.

*Anemia.*—This disease has been observed after chronic irradiation of the bone narrow from external sources (20, 27) or from radioelements deposited in bone (46). It has also been noted as a long-delayed complication of radiotherapy (66). Experimental data indicate that the marrow damage may be repaired by transfusion of viable, nonirradiated hemopoietic cells (42). Although there has been much study of the *acute* destruction of the bone marrow that occurs within the first month after irradiation, little is known of the development of aplasia and fibrosis as a *delayed* sequel. Martland (47) emphasized that in radium-

poisoned dial painters the anemia was accompanied initially by proliferation of primitive hemopoietic cells in the bone marrow, aplasia and fibrosis occurring only late in the disease. Unfortunately, as stressed by Mole (49) investigation of this condition is hampered by difficulty in assessing the extent of radiation damage of the bone marrow from examination of the peripheral blood alone.

*Radiation Dermatitis.*—This was one of the first radiation injuries to be recognized. It develops insidiously, as a result of overexposure of the skin to penetrating radiations. In association with the degenerative changes in the epidermis and dermis, there is a tendency toward epidermal neoplasia. The martyrdom of many of the early radiologists to radiation-induced cancer of the skin was recorded by Brown (8).

*Radiation Osteitis.*—Martland (47) introduced the term "radiation osteitis" to denote the destructive process produced in bone by internally deposited radium. This condition develops slowly and after many years leads to such complications as necrosis of the mandible and maxilla, pathologic fracture, and osteogenic sarcoma. The clinical, radiologic, and pathologic features have been reviewed by Aub and associates (2) and by Looney (40).

*Radiation Sterility.*—Depression of gametogenesis in the testis or ovary through the killing of germ cells or their precursors causes radiation sterility. The most radiosensitive cells are the spermatogonia and the developing ova; the former are killed in significant numbers by less than 5 r of X-rays in the mouse (53). Mature spermatozoa and ova are less radiosensitive, however, and may persist for a time after irradiation, preventing the immediate onset of sterility despite cessation of gametogenesis. After the supply of preformed germ cells becomes exhausted, sterility ensues but is permanent only when the primitive precursors have been destroyed to the extent that regeneration and resumption of gametogenesis do not take place. In general, the amount of radiation required to cause permanent sterility is apparently within the lethal range if administered to the entire body at one time; hence permanent sterility is not generally a complication of whole-body irradiation, except in the female mouse (13).

It must not be forgotten that genetic damage, such as gene mutation, is also induced by radiation in germ cells. This form of injury is inevitably passed on in the germ line and may seriously and irrevocably affect countless subsequent generations of progeny (51, 55). Unlike sterility, genetic damage is thought to occur in response to the smallest amounts of radiation, varying in proportion to the total accumulated dose.

*Radiation Cataract.*—Considerable attention has been paid to radiation cataracts since the discovery of radiation-induced lens opacities in otherwise healthy people occupationally exposed to relatively small amounts of neutron radiation from cyclotrons (1). Extensive clinical and experimental studies of this lesion indicate that it results primarily from injury of the cells of the anterior epithelium of the lens, neutrons being significantly more damaging to this tissue than X or gamma rays (61). Another occular degenerative change, atrophy of the iris, has been induced by irradiation (3). Like radiation cataract, this process develops spontaneously in aging mice of the $LAF_1$ strain, but in irradiated animals it occurs earlier and is more severe in proportion to the amount of radiation received.

Since cataract and iris atrophy can be produced by localized irradiation, they obviously do not entail aging of the organism as a whole Their resemblance to changes that occur naturally in old age may not be fortuitous, however, since whole-body irradiation causes degenerative alterations of other tissues commensurate with accelerated aging. For example, irradiated mice dying prematurely exhibit generalized atrophy of parenchymatous organs; weight loss; debilitation; untidiness and thinning of the fur; diminished alertness, inquisitiveness, and physical activity; and other outward appearances of senility. Hence it is conceivable that degenerative changes caused by localized irradiation may be analogous to localized aging, since from clinical experience it is evident that spontaneous aging does not affect all organs to the same extent in all people.

## RADIATION-INDUCED AGING

Analysis of autopsy data has disclosed that irradiated animals (64) and human beings, i.e., radiologists (65), apparently die prematurely from nearly all causes and not merely from those manifestly related to radiation injury.

Although neither radiation injury nor aging is well understood, aging itself has been interpreted as the *accumulation of the effects of nonspecific injuries* sustained throughout life (15,

34). To account for the life-shortening action of ionizing radiation, it has been postulated that irradiation initiates a process of lethal injury that is a weighted sum of the various kinds of physiologic damage produced (57). Another mechanism has been suggested by Harman (29), who has attributed the degenerative changes to the deleterious effects of free radicals on protoplasmic constituents.

The possibility that *somatic mutations* cause natural and radiation-induced aging deserves consideration. Owing to the presence of billions of cells in the body, a sizeable number of mutations are inevitably accumulated by an individual during a lifetime. Since these mutations are for the most part deleterious, their effects will be the death or the subnormal function of the affected cells and their derivatives, the end result of this cumulative process being diminished vitality of the organism, or senescence. This hypothesis has been stated in terms of information theory by Yockey (67). It is noteworthy that the effects of irradiation on the life span are relatively cumulative, or "irreparable," (6); this is consistent with an underlying genetic or chromosomal mechanism, particularly in view of the known mutagenicity of ionizing radiation (51). If the genetic hypothesis of aging is proved valid, it is significant that in microorganisms some genetic effects of radiation, heretofore considered irreversible, are now known to be susceptible to modification before, during, or after irradiation (32).

Mice, likewise, may be afforded marked protection against the delayed, life-shortening effects of radiation by techniques now being developed, i.e., injection of protective chemicals, such as cysteine, before exposure and by anoxia and shielding of hemopoietic cells during exposure (33).

## EFFECTS OF RADIATION ON LIFE SPAN OF DESCENDANTS

Not only does irradiation reduce the length of life of the individuals exposed, but it may affect the longevity of their descendants as well. A significantly diminished longevity was noted in the $F_1$ offspring of male mice mated 19-23 days after whole-body neutron irradiation (56). This effect, which resulted, presumably, from radiation-induced mutations or other genetic injuries in the sperm, is not surprising in view of the known influence of genetic factors on longevity (15).


## SUMMARY

The life span is shortened by exposure to ionizing radiation in proportion to the amount of radiation absorbed.

The life-shortening action of radiation involves the induction of neoplasia and nonneoplastic degenerative changes and simulates in many respects acceleration of the natural aging process.

The capacity of ionizing radiation to accentuate changes associated with senescence indicates its usefulness as an agent in the experimental investigation of aging.

Further study should be directed toward the detailed comparison of senescence in irradiated and nonirradiated organisms.


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# BOOK REVIEWS

PROBLEMS OF AGING. A Symposium presented at the Twenty-eighth Annual Graduate Fortnight of the New York Academy of Medicine, October, 1955, edited by Robert L. Craig, M.D., distributed by George Eliot, New York, 1956. 221 pages, paper bound.

It is noteworthy that the title of this book is the same as that of the Symposium presented at the First Graduate Fortnight in 1928. The publication includes 19 lectures dealing with subjects within the fields of gerontology and geriatrics.

A. Lansing raises the question "What is Aging?" and emphasizes the significance of research in this field, pointing out that the biologic research on aging of today constitutes the geriatrics of tomorrow. Psychologic and psychiatric aspects of aging are discussed by R. McFarland and F. Braceland. C. McCay and his associates report experiments on the prolongation of the life span and on parabiotic union between rats. J. Bunam gives a clinical review of osteoarthritis in old individuals and W. Dock outlines the aspects of aging of the myocardium.

The chapter by N. Shock on physiologic aspects of aging is read with great interest. The subjects reviewed by Shock include acid-base equilibrium; blood glucose level; total blood and plasma volumes; vitamin A plasma level; eosinophil response to ACTH; basal heat production; and Shock's detailed studies on kidney function.

F. Stare calls attention to the significance of proper nutrition in old individuals. T. Almy, D. Rosmean, and W. Braveman discuss the subject of gastrointestinal hemorrhage in elderly patients with peptic ulcer, hiatus hernia, and diverticulitis. J. Whittenberger surveys the nature of the response to stress with aging. He concludes that the impairment with age is a real one, but that the results of the impairment are not necessarily serious. Much could be done in preservation of function of the elderly, if attention was directed towards maintenance of high levels of mental and physical ability. D. Richards evaluates pulmonary function and emphasizes that the aging lung is remarkably adequate and efficient, and that certain lung conditions of an atrophic and degenerative type are of importance in the pathogenesis of certain chronic disease states.

The very important subject of geriatric surgery is illustrated through a series of very valuable papers. H. Randall, K. Roberts, and J. De Cosse discuss fluid and electrolyte problems in surgery, and J. La Due reviews the evaluation and preparation of the patient with degenerative cardiovascular disease. Papers by R. Kennedy and by C. Cutler deal with the management of injuries and surgical emergencies in old patients. The subjects of surgery and anesthesia in the aged are reviewed by F. Glenn and by E. Papper. Experience from the last few years indicates the occurrence of fewer postoperative complications and a lower surgical mortality; this seems especially to be the case when one is not dealing with emergency operations and when opportunity is provided for proper presurgical treatment of the elderly patients.

In the concluding chapters I. Cooper describes his neurosurgic procedure for alleviation of Parkinsonism, and H. Rusk and M. Dacso emphasize the great importance of rehabilitation in the aged.

The collection of papers composing the symposium constitutes most interesting reading material and convincingly demonstrates the high level of gerontology and geriatrics in the United States.

TORBEN GEILL, M.D.
De Gamles By
Copenhagen, Denmark

CARE OF THE LONG-TERM PATIENT. Chronic Illness in the United States—Volume II. Harvard University Press, Cambridge, 1956, 606 pages, $8.50.

This book is a major contribution to the information that we are acquiring slowly and rather painfully about chronic illness and its impact on our society. It should have a prominent place as a reference work on the bookshelves of workers in the health and welfare professions, educators, and governmental officials.

In 1949, four national organizations (American Hospital Association, American Medical Association, American Public Health Association, American Public Welfare Association) concerned with the magnitude of the problems of chronic disease, illness, and disability, founded the Commission on Chronic Illness, with a membership of over 40 distinguished professional and lay citizens. This Commission, assisted by a technical staff, defined the scope of the problem, developed a philosophic approach, and amassed and integrated information about problems arising from long-term illness. *Care of the Long-Term Patient* is an outgrowth of a major project of the Commission, which was a National Conference on Care of the Long-Term Patient in 1954.

Most of the material in the book has been available heretofore in bits and pieces. However, viewed from the perspective that it brings together in orderly fashion the distillation of thinking of many groups and individuals about that segment of the chronic illness problem that deals with the care of the patient, it is a significant and original document.

Discussion of who the long-term patient is, where he may be found, and the variety of his needs for care is followed by detailed consideration of his treatment in the home and in the various institutions that are available to him: Chronic disease hospitals, general hospitals, nursing homes, homes for the aged, mental institutions, and institutions for the handicapped child. The good features and inadequacies of each resource are evaluated.

Other sections deal with requirements for medical and other health personnel to care for the chronically ill patient, with need for coordination and integration of effort by the many groups at all levels of governmental and private organization who serve this type of patient, and with the role of research. A final chapter

reviews the methods of financing now available for paying the cost of care of the long-term patient, and hopefully suggests how this over-riding problem can be solved.

All of the material is summarized into 80 conclusions and recommendtaions. Inevitably they are general in tone, emphasizing what should be done rather than how to do it. Taken as a whole, they present a broad program of action for all who are concerned with the chronic patient.

DAVID LITTAUER, M.D.,
Executive Director
Jewish Hospital of St. Louis

BOOKS RECEIVED

*Connective Tissue in Health and Disease*, edited by G. Asboe-Hansen, Ejnar Munksgaard, Copenhagen, Philosophical Library, New York, 1957, 321 pages, $15.00.

*Current Therapy 1957*, Latest Approved Methods of Treatment for the Practicing Physician, edited by Howard F. Conn, W. B. Saunders Company, Philadelphia, 1957, 731 pages, $11.00.

*Problems of Aging*. A Symposium Presented at the Twenty-Eighth Annual Graduate Fortnight of the New York Academy of Medicine, October, 1955, edited by Robert L. Craig, M.D., distributed by George Eliot, New York, 1956, 221 pages, paper bound (reviewed in this issue, page 314).

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# Section B

## Psychological and Social Sciences, Social Welfare

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# SOME EFFECTS OF AGE ON THE QUALITY OF INTELLECTUAL OUTPUT

DENNIS B. BROMLEY, B.A.

*(From the Department of Psychology, University of Liverpool, England)*

In a previous report (1) the author outlined some of the relationships between chronologic age and quantity and quality of output on a performance test of conceptual thought using Lehman's conclusions (5) as experimentally testable hypotheses. The present study is a further attempt to explore the nature and scope of age differences in higher intellectual processes and to relate the facts of normal intellectual decline with age to the facts of the pathology of thought.

Wegrocki (14) studied disturbances of the higher intellectual processes in schizophrenia and used three verbal tests specially designed to measure generalizing ability: (a) Proverbs, in which meanings were generalized to a more abstract semantic level, (b) Differences, in which relations were generalized under conceptual categories, and (c) Analogies, in which relations were generalized into a schematic framework. All three tests were thought to involve comparison, juxtaposition, selection and recombination into more inclusive wholes, i.e., generalization. The proverbs test consisted of 7 items demanding the matching of two proverbs and an explanation; it had a test-retest reliability of 0.55 on 40 normal adults and 0.63 on 40 normal boys; the time interval for retest, however, was not given. Wegrocki found that younger children and schizophrenics tended to use superficial criteria in matching the proverbs, but there were qualitative differences, e.g., the degree of relevance, in the types of error they made. It seemed to be the case that thought disorder in schizophrenia represented a disrupting, fractionating process rather than a regression to an earlier or more primitive developmental level.

Rylander (8) studied personality changes after operations on the frontal lobes by asking the patients to explain the meanings of 10 proverbs; in general, their responses were very concrete. The patients seemed to be incapable of recognizing the abstract significance of the situations given in the proverbs and unable to extricate themselves from the given situation; this led them to draw entirely wrong conclusions. They tended to respond by relating anecdotes and they sometimes gave explanations which could be described as concrete, literal, of limited significance, or not appropriate.

Thurstone (11) described two reading tests in his Primary Mental Abilities Test and said that they were used as part of Thorndike's (10) CAVD test. The items call for the interpretation of proverbs and of quotations with paraphrased statements, so that the subject makes a fairly large number of objective responses in which he must interpret meanings and not merely repeat statements. When interpreting the factors, Thurstone seems to say that both tests are essentially verbal and logical in character, and that the only primary mental ability entering into the interpretation of proverbs and quotations to any significant degree is V (verbal relations).

Hall (4) used proverbs in his work on abstraction impairment in schizophrenia. He claimed that proverbs tests often bring out irrelevancies of thinking which are not apparent from other tests. The responses of the schizophrenics were characterized by irrelevance, simplification, and concreteness—a result similar to that obtained by Wegrocki (14).

Study of the pertinent literature leads one to believe that proverbs tests are valid measures of higher thought processes (9, pp. 283-284) and that performance on them is disrupted in characteristic ways by a number of strictly pathologic states. The questions we hope to answer in the present inquiry are: (a) Is increasing age after maturity in normal people associated with an impairment of proverb interpretation? and (b) If there is a significant amount of impair-

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This report is based on a paper read to the Annual General Meeting of the British Psychological Society, 1956. Appreciation is given to Dr. T. Renshaw of Moray House who directed attention to a number of sources of information about proverb-items in intelligence tests, and to colleagues at the University of Liverpool Department of Psychology and the Medical Research Council Group for Research on the Occupational Aspects of Ageing for their advice and criticism. Full details of both tests described in this report may be obtained from the author.

ment, will it be similar to or different from the impairment characteristic of pathologic states?

The findings of Lehman (5) and the author (1) prompted the latter to propose the following theory to account for the normal decline with age in quantity and quality of intellectual output. There is (a) an impoverishment of *performance potentialities*, especially a recession of what Cattell (2) would call fluid ability, and (b) an impairment of *performance evaluation*, i.e., a breakdown of the self-critical attitude towards one's thinking. The distinction between performance potential and performance evaluation, which seems to have been made first by Rashkis (7) in connection with his work on psychiatric patients, seems to be an invaluable distinction to bear in mind when trying to make sense of the complicated age changes and age differences in intellectual processes. Performance potential refers to a person's capacity for producing ideas of various kinds quickly and in large numbers; performance evaluation refers to a person's capacity for discriminating between good ideas and bad ones, for testing these ideas against reality, for rejecting them if they are unrealistic or wrong, and for instigating their modification or replacement.

Both performance potential and critical evaluation are necessary for sane productive thinking, and both decline with age. The nature and scope of age impairment in performance potential have been explored by Wechsler (13) and many others, but relatively little attention has been paid to the problem of age impairment in performance evaluation, i.e., to age changes in the quality of intellectual response. Referring back to Lehman (5) and Bromley (1), there is evidence to suggest that the decline in performance potential is expressed as a *gradual* fall-off with age in the *quantity* of intellectual output, and that the decline with age in performance evaluation is expressed as a relatively *rapid* fall-off with age in the *quality* of intellectual output. To put the matter in its simplest form and without qualification we can say that as we grow old we become not only less able to produce ideas but also less able to judge their worth.

From this theory it should follow that even if the quantity of intellectual output is held constant with age experimentally by having all the subjects in the different age groups answer all the items in a test, as was the case in the present investigation, yet an increase in age after maturity will be associated with a decrease in the quality of that output.

## METHODS AND RESULTS

Two tests of proverb interpretation were prepared. The first, which will be called the *creative response test*, consisted of 14 proverbs of the type, "You must not cast pearls before swine." After appropriate instructions, the subjects were asked to explain the meaning of each proverb. No time limit was imposed and ambiguities in the subjects' responses were cleared up by non-directive questions. Each interpretation was scored as follows: 2 points for an abstract and generalized explanation in which the principle was clearly explained; 1 point for an explanation which was relevant but failed to reach an abstract level or failed to generalize the principle sufficiently; no points for any kind of failure, i.e., concrete, literal, or anecdotal explanations, confused and irrelevant associations, misinterpretations, and "don't knows." For example, the following interpretations to the proverb mentioned above would be scored 2, 1, and 0, respectively: "Don't waste valuable things on unappreciative people," "Some people don't appreciate beautiful things," and "Don't give money to spendthrifts. They (the pearls) would be wasted."

The second, which will be called the *multiple choice test*, was also untimed and consisted of 10 proverbs printed on separate cards. Underneath each proverb were three explanations of the meaning of the proverb lettered (a), (b), and (c). After appropriate instructions the subject was asked to write down on the record-form the letters indicating the "best," "next best," and "worst" explanation for each proverb. Each group of three explanations contained one abstract or general interpretation, one functional interpretation or an interpretation which was relevant but insufficiently abstract and general, and one concrete or literal interpretation. Thus, the responses to both the *creative response* and the *multiple choice* tests were scored according to their quality and classified according to a system developed by Rapaport and associates (6) in another connection. The scoring of the multiple choice test was as follows: 2 points for each correctly identified explanation, 1 point for a slight error of judgment, e.g., identifying an explanation as worst instead of next best, no points for

a major error of judgment, e.g., identifying an explanation as worst instead of best. Item 3 on the multiple choice test was, "Don't count your chickens before they are hatched," for which the abstract and general, i.e., the best, explanation offered was, "Expectations are not always fulfilled." The functional or limited explanation, i.e., the next best, was, "Don't look too far ahead," and the concrete or literal explanation, i.e., the worst, was, "Not all eggs hatch out into chickens."

Quality of intellectual response can be defined operationally in terms of performance on the two proverbs tests; this performance may be measured in three ways: (a) the total score on a test when the answers are scored 2, 1, or 0 according to their merit, (b) the proportions of answers classified as good, 2, medium, 1, or poor, 0, and (c) the proportions of errors classified as normal (E1) or abnormal (E2). The statistical procedure and notation will be as recommended by Walker and Lev (12).

The two proverbs tests formed part of a large battery of tests administered to samples of subjects of different ages in an investigation designed to explore some of the complex and interesting relationships between normal aging and higher thought processes. The other tests in the battery measured various aspects of intelligence and conceptual thought; they will be reported on at a later date and need not be discussed in this report. Altogether 256 subjects between the ages of 17 and 82 years of age were tested; they were recruited from several sources but represented mainly the higher levels of intelligence and socio-economic status. Split-half reliability coefficients for both proverbs tests were computed and corrected to full length and gave 0.90 for the creative response and 0.73 for the multiple choice test. The product-moment correlation between the two tests was +0.54 (+0.45 with age held constant, and +0.56 when corrected for age and attenuation). In spite of their superficial similarity in content therefore it must be concluded that the two tests measure rather different intellectual functions. This is not surprising considering that the form as well as the content of a test determines the way in which it will be handled. It is to be expected that the correlation between the tests would increase if they were lengthened and improved.

It may be asked why the correlation is not higher if both tests are measuring performance evaluation. The answer to this question is that (a) no claim is made that the tests are relatively pure or even particularly good tests of performance evaluation, and (b) performance evaluation may be a collection of special abilities and attitudes and not a general trait, so that there may be different ways of assessing it. Although quality of intellectual output seems to be closely related to performance evaluation, yet this is not to say that it is unrelated to performance potential—obviously both performance evaluation and performance potential play a part in the final product, both the amount and the quality. According to Lehman (5), for example, quality and quantity of output are positively but imperfectly correlated, and they may be differently related to other variables like age and experience. Similarly, performance evaluation and performance potential may be positively but imperfectly correlated and this may help to account for the lack of correlation between the two proverbs tests—performance on them may be determined in different ways and in different degrees by both performance evaluation and performance potential.

In order to explore age differences in intellectual performance on the two proverbs tests, subjects were selected from the pool of 256 subjects in such a way as to build up three groups differing in chronologic age but matched in respect to other relevant variables. The groups were made as large as possible consistent with the aim of establishing precise controls, *i.e.*, by matching, for Wechsler-Bellevue IQ (Full Scale), Wechsler-Bellevue Vocabulary (Raw Score), and Social-Background Rating (1) (See table 1).

Sex differences were eliminated on the independent variables during the process of selecting matched groups. There are approximately the same number of men and women in each age group. No sex differences were observed on the dependent variables, i.e., on proverbs test scores, and statistics will not be given separately for men and women. Table 2 shows one way of demonstrating the relationship between age and quality of intellectual output.

The evidence gives clear support to the hypothesis that when answers to tests of proverb interpretation are scored according to their quality an increase in chronologic age after maturity will be associated with a decrease in score. Strictly speaking, this generalization

TABLE 1. COMPARISON OF THREE MATCHED AGE GROUPS.

| Group | N | Age | | Wechsler-Bellevue IQ | | Wechsler-Bellevue Vocabulary | | Social Background Rating | |
|---|---|---|---|---|---|---|---|---|---|
| | | $\bar{X}$ | $s^2$ | $\bar{X}$ | $s^2$ | $\bar{X}$ | $s^2$ | $\bar{X}$ | $s^2$ |
| A | 61 | 27.0 | 26.9 | 122,0 | 49.3 | 30.3 | 16.3 | 2.9 | 0.6 |
| B | 71 | 46.5 | 27.0 | 122.6 | 61.9 | 31.3 | 17.7 | 2.8 | 0.9 |
| C | 68 | 66.5 | 26.0 | 120.9 | 62.8 | 31.3 | 21.1 | 2.7 | 0.8 |
| Total | 200 | 47.4 | 279.4 | 121.8 | 58.3 | 30.0 | 18.5 | 2.8 | 0.8 |

Observed values of $F_{max}$, and F in analysis of variance tests on Table 1 confirm that the three groups, A, B, and C, differ significantly in mean age, but do not differ significantly in age variance or in mean and variance for Wechsler-Bellevue IQ, Wechsler-Bellevue Vocabulary (raw score), and Social-Background Rating.

holds only within the limits set by the samples and the tests involved, but it seems to give an additional pointer to the general nature of normal intellectual decline with age.

Table 3 shows another way of demonstrating the relationship between age and quality of intellectual output: the proportions of good, 2, and poor, 0, answers change systematically and significantly as age advances. The character of the age difference is interesting since the youngest age group (A) gets considerably less and the oldest age group (C) considerably more than the expected number of poor, 0, answers; conversely, the youngest age group (A) gets considerably more and the oldest age group (C) considerably less than the expected number of good, 2, answers.

On the creative response test, errors, scoring 0, were classified into two main sorts: (E1) comprising misinterpretations and "don't knows"—these were considered to be normal errors, and (E2) comprising concrete and literal explanations, anecdotes, confused and irrelevant associations—these were considered to be abnormal errors, i.e., they seemed to be deteriorated or primitive. Table 3 shows not only that the total number of errors, i.e., poor, 0, answers, on the creative response test increases with age but also that the quality of the errors deteriorates with age, i.e., there is a slight decline with age in the frequency of normal errors of interpretation, but there is a marked increase with age in abnormal errors. The observed age differences in the proportions of normal (E1) and abnormal (E2) errors are statistically significant. The following explanation is put forward tentatively: (E1) errors result from ignorance and lack of intelligence, i.e., from a lack of performance potentialities; (E2) errors result from some sort of falling away from an abstract or a conceptual point of view toward a more primitive, concrete, or disorganized level of thinking (cf. 3), i.e., from a lack of performance evaluation. Errors of the second type (E2) of course are those described by other investigators as characteristic of the psychiatric patient with intellectual impairment.

TABLE 2. COMPARISON OF THREE MATCHED AGE GROUPS, TOGETHER WITH STATISTICAL TESTS OF THE RELATIONSHIP BETWEEN MEAN SCORE AND AGE, WHERE ANSWERS ARE SCORED EITHER 2, 1, OR 0 ACCORDING TO THEIR MERIT.

Creative Response Test

| Age Group | $\bar{X}$ | $s^2$ | Analysis of Variance | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | Source | Sum squares | n | Mean square | F | $F_{.99}$ |
| A | 18.74 | 13.30 | | | | | | |
| B | 17.73 | 31.37 | Total | 5987.68 | 199 | | | |
| C | 14.79 | 36.43 | Between means | 552.68 | 2 | 276.34 | 10.02 | 4.71 |
| Total | 17.04 | 30.09 | Within groups | 5435.00 | 197 | 27.59 | | |

Multiple Choice Test

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| A | 53.54 | 17.79 | | | | | | |
| B | 50.03 | 26.46 | Total | 7184.00 | 199 | | | |
| C | 46.79 | 41.81 | Between means | 1463.79 | 2 | 731.90 | 25.20 | 4.71 |
| Total | 50.00 | 36.10 | Within groups | 5720.21 | 197 | 29.04 | | |

Analysis of variance in Table 2 demonstrates that for both proverbs tests the means of age groups A, B, and C are unequal, for in both cases the observed value of $F > F_{.99}$.

TABLE 3. COMPARISON OF AGE GROUPS ON DIFFERENT RESPONSE CATEGORIES.

| Statistic | Age Group | Response Category | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Multiple Choice Test | | | | Creative Response Test | | | | | | |
| | | 2 | 1 | 0 | Total | 2 | 1 | 0 | Total | E1 | E2 | Total |
| ΣX | A | 1453 | 360 | 17 | 1830 | 365 | 413 | 76 | 854 | 51 | 25 | 76 |
| | B | 1497 | 558 | 75 | 2130 | 393 | 473 | 128 | 994 | 49 | 79 | 128 |
| | C | 1266 | 650 | 124 | 2040 | 272 | 402 | 218 | 952 | 36 | 182 | 218 |
| | Total | 4216 | 1568 | 216 | 6000 | 1030 | 1348 | 422 | 2800 | 136 | 286 | 422 |
| Σ(X)% | A | 79.4 | 19.7 | 0.9 | 100 | 42.7 | 48.4 | 8.9 | 100 | 67.1 | 32.9 | 100 |
| | B | 70.3 | 26.2 | 3.5 | 100 | 39.5 | 47.6 | 12.9 | 100 | 38.3 | 61.7 | 100 |
| | C | 62.1 | 31.9 | 6.0 | 100 | 28.6 | 48.5 | 22.9 | 100 | 16.5 | 83.5 | 100 |
| | Total | 70.3 | 26.1 | 3.6 | 100 | 36.8 | 48.1 | 15.1 | 100 | 32.2 | 67.8 | 100 |
| $\bar{X}$ | A | 23.8 | 5.9 | 0.3 | 30 | 6.0 | 6.8 | 1.2 | 14 | 0.8 | 0.4 | 1.2 |
| | B | 21.1 | 7.9 | 1.0 | 30 | 5.5 | 6.7 | 1.8 | 14 | 0.7 | 1.1 | 1.8 |
| | C | 18.6 | 9.6 | 1.8 | 30 | 4.0 | 6.8 | 3.2 | 14 | 0.5 | 2.7 | 3.2 |
| | Total | 21.1 | 7.8 | 1.1 | 30 | 5.2 | 6.7 | 2.1 | 14 | 0.7 | 1.4 | 2.1 |
| $s^2$ | A | 14.9 | 12.7 | 0.4 | – | 5.6 | 3.0 | 2.6 | – | 1.6 | 0.6 | 2.6 |
| | B | 17.9 | 12.5 | 1.6 | – | 10.7 | 5.7 | 7.8 | – | 1.4 | 5.2 | 7.8 |
| | C | 23.8 | 14.7 | 4.2 | – | 9.4 | 5.2 | 11.4 | – | 0.7 | 10.7 | 11.4 |
| | Total | 23.2 | 15.3 | 2.5 | – | 9.3 | 4.7 | 8.0 | – | 1.2 | 6.5 | 8.0 |

Observed values of $\chi^2$ based on the figures for $\Sigma X$ in table 3 are as follows: (i) for the multiple choice test, when $n = 4$ the observed $\chi^2 = 167.2 > \chi^2_{.99}$, (ii) for the creative response test, when $n = 4$ the observed $\chi^2 = 91.3 > \chi^2_{.99}$, and (iii) for the errors on the creative response test, when $n = 2$, the observed $\chi^2 = 69.1 > \chi^2_{.99}$. The reading of Table 3 will be facilitated if it is remembered that, (a) there are 30 responses to the multiple choice test since each of 10 proverbs has 3 alternatives to be ranked, (b) there are 14 responses to the creative response test, (c) there is no variance for the total score on either test since all the Ss responded to exactly the same number of items, i.e. to all of them, and (d) there were 200 Ss altogether giving a total of 6000 responses to be classified on the multiple choice test and 2800 on the creative response test.

The validity of the Chi-square analysis of the two proverbs tests may possibly be criticized because a number of obseravtions is made on the same person, i.e., 30 for the multiple choice and 14 for the creative response test, so that the observations may not be truly "independent." This criticism implies that we cannot be sure that, for example, 30 observations made on each of 200 subjects would have the same distribution as 1 observation made on each 6000 subjects, even if the subjects in both instances are drawn from the same population. Be this as it may, there is an alternate method of testing the null hypothesis that scores on the proverbs tests are independent of age that is not open to the same objection. The alternative method is the non-parametric Median Test for a comparison of k samples. The raw-score totals for each S in each age group on each proverbs test can be classified according to whether they fall above or below the median (or the score nearest the median), as in table 4.

TABLE 4. COMPARISON OF AGE GROUPS IN TERMS OF THE NUMBERS OF SUBJECTS SCORING ABOVE THE MEDIAN (+) OR BELOW THE MEDIAN (−) ON TWO PROVERBS TESTS.

| Age Group | N | Multiple Choice Test | | Creative Response Test | |
|---|---|---|---|---|---|
| | | + | − | + | − |
| A | 61 | 46 | 15 | 38 | 23 |
| B | 71 | 36 | 35 | 39 | 32 |
| C | 68 | 18 | 50 | 24 | 44 |
| Total | 200 | 100 | 100 | 101 | 99 |

Observed $\chi^2 = 30.84$. Observed $\chi^2 = 10.24$
When $n = 2$, then $\chi^2_{.99} = 9.2$

In both cases the observed Chi-square is greater than $\chi^2_{.99}$. Therefore the null hypothesis, which says that age is unrelated to performance on the proverbs tests, must be rejected, and we can conclude that age in fact seems to have an adverse influence on the quality of performance in both tests.


## SUMMARY

A creative response test and a multiple choice test of proverb interpretation were administered to three different age groups matched on several relevant variables. A study of the pertinent literature suggested that proverb interpretation was a useful way of testing higher intellectual processes; deteriorated psychiatric cases responded in ways variously described as irrelevant, concrete, anecdotal, literal, inappropriate, of limited significance, and oversimplified. A theory of normal intellectual decline with age was proposed in which the overall impairment is said to be due to (a) a loss of performance potentialities, which govern mainly the quantity of output, and (b) a loss of performance evaluation, which governs

mainly the quality of output. From this it was deduced that if the quantity of output was kept constant experimentally, by giving the subjects an opportunity to offer interpretations for all the proverbs, then an increase in age after maturity should be associated with a decrease in quality of output. Quality of output was defined in terms of the conceptual level of interpretation and in terms of the type of error. Statistical tests on the observed data confirmed the deduction, and it was found that the types of error which increased in frequency from one age group to the next were those also characteristic of psychiatric cases with intellectual impairment.

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# A PROPOSED PLAN FOR OLD AGE SECURITY INSURANCE

FRANCES GILLESPIE SCOTT

*(From the Department of Anthropology and Sociology, University of California, Los Angeles)*

The social and economic importance to the United States of a steadily aging population is no longer a problem which can be solved by individuals or even by communities, acting alone; cognizance of this fact on the part of academicians and businessmen alike is increasingly demonstrated in recent publications (1, 6, 10, 11, 12). Two very important aspects of the total problem of the aged, from the viewpoint both of the older people themselves and the communities in which they live, are the interrelated questions of dependency and housing. Dependency is one of the most important problems in urban communities, and slightly more than 85 per cent of the population aged 65 and over lived either in urban or rural non-farm communities in 1956 (13). If people could provide for themselves during their earning years an income sufficient for an adequate standard of living when they grow old, the solution of many of the other problems of aging would be advanced significantly.

The extent of the problem at present and the enormity it will reach in the very near future can best be understood by consideration of the size and composition of the population now thought of as aged, the income of this population, and an examination of living conditions for this group.

1) The total population of the United States almost doubled between 1900 and 1950; the percentage of persons aged 65 and over also doubled—from about 4 per cent to a little over 8 per cent—but the actual number of aged persons quadrupled. In addition, the percentage of people who are middle-aged, i.e., between 45 and 64 years, almost tripled during the same time; in 1950, there were 30½ million in this age group (5).

2) Demographers will not hazard unqualified opinions about the future behavior of the American birth rate; however, it has been estimated (1, p. 5) that if high fertility and low mortality rates, such as are presently operating, continue until 1960, there will be 23½ million people aged 60 and over in the U. S., or 13.7 per cent of the estimated total population. Even under a condition of low fertility and high mortality there will be over 22 million persons in this group, or 13 per cent of the population.

3) The common-sense observation that women live longer than men is borne out by census figures (5). The sex ratio steadily declined from 1900, and in 1950 there were only 89 men per 100 women. This is partly due to higher mortality rates in all age groups for males than females, and partly due to immigration restrictions since 1920. Nevertheless, the average husband today can quite confidently expect that his wife will outlive him by several years; he can be almost equally confident that she may spend the last years of her life in a state of dependency. In 1950, only about one-third of the population aged 65 and over was self-supporting (7). The remainder of the 13 million people in this age group were dependent upon relatives,, savings, government funds, pensions, or other persons. In 1955, there were about 3 million persons aged 65 and over with no money income at all, and of these over 2½ million were women (11, p. 28, 14, p. 13), although probably about half of them lived with their husbands, who might have had some income. In 1950, 76 per cent of the unrelated individuals in this age group had less than $1,000 annual income, and there were almost 2½ million such persons, not including those with no income at all (15, p. 25). Families in which an aged person is the head are in only slightly better circumstances. Over half of these had less than $2,000 income in 1950; a little more than 30 per cent of them received less than $1,000 (5, pp. 16, 20, pp. 49-50). Although considerable progress has been made to reduce the number of the aged who have no income at all, through such measures as the eligibility of larger numbers of people for Old Age and Survivors Insurance benefits, there are still large numbers of persons with no money income, and these are primarily widows.

4) In 1951, employment contributed the largest single source of income, to over 30 per cent of the aged population (5, p. 53). Old Age and

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Survivors Insurance benefits, in 1951, were for the first time received by more persons than received Old Age Assistance; about 25 per cent, or some 3,300,000, received an average monthly benefit of $42.00 (1, pp. 154-163). While these benefits have recently been raised, there is grave doubt among some economists that payroll taxes can be depended upon to finance a really adequate program without serious effects upon the national economy (11, pp. 32-37). Even with recent extensions to previously uninsured persons, O. A. S. I. alone does not seem to be the solution to the financial problems of the great number of aged persons who will be living in the United States in the foreseeable future.

5) Despite restricted income, in 1950 almost 70 percent of the aged maintained their own homes, even to the point of sacrificing an unduly large portion of their income to do so. Many of the homes were inconvenient and unsafe. While a significant number owned their homes, finding low-cost rental housing was a problem to many, particularly in large cities (1, pp. 126-138). Most of the group lived either with a spouse or had a relative living with them. When this was not the case, they lived in the homes of relatives. It is quite evident that the aged prefer to live in families, either their own or that of someone else. Only about 6 per cent were in institutions (5, p. 14). Over twice as many women as men lived alone in 1950, and twice as many men as women were still living with a spouse in their own homes. Still, 8 out of 10 men and 7 out of 10 women lived in a family situation, even though more women than men lived in the homes of relatives or others.

In considering the two aspects of dependency and housing, we see in both areas only partial solutions have been offered. The magnitude of the problems of the aged preclude easy solutions. The plan outlined here would again provide only a further partial solution to these problems, but it is capable of coordination with existing portions to comprise a more nearly complete answer. The aim is to enable the employed, adult individual an opportunity to provide more adequately for his own old age during the years when his income is at its peak.

## THE PROPOSED OLD AGE SECURITY INSURANCE

For several decades, insurance companies have offered various retirement insurance plans to the public, and through nation-wide advertising in popular publications these insurance plans have been presented as a sound investment for a secure old age. Nearly all business and industrial organizations, with the exception of those having a very small number of employees, offer as fringe benefits group life insurance programs, but these are not retirement programs. The matter of retirement and pensions is usually handled by special funding on the part of the company (2, 9, pp. 21-23). There are two very obvious limitations to such plans: 1) the coverage is neither continuous nor transferrable when the employee changes his job, except in rare instances, and 2) the cost of the plan ultimately comes from company profits, even though the employee contributes to the cost during his period of employment. To date, there are so few retired persons receiving benefits from such plans that the effects on the national economy have been slight. It may be quite different when several million employees have retired, and when pensions must be paid to former employees for 10 to 20 years after they have retired.

Life insurance companies have been offering a variety of endowment policies, aimed primarily at the professional and semi-professional worker and the self-employed. It is true that the majority of the 20-year-pay policies are within the reach of the American middle-class; but it is difficult to convince the average man that while it is obviously desirable to buy life insurance to protect his wife and children, he himself may very likely live long enough to face the problem of keeping up the premiums on a straight-life policy and still provide food and shelter for himself and his wife.

An effort has been made by life insurance companies to meet this problem. There are straight-life policies which may be converted to endowment insurance when the children grow up. Another plan is the endowment policy which provides for payment of a premium for something like 15 or 20 years, it is then considered paid up and endows at age 65 or some other suitable retirement age. The insured then has the choice of several optional settlements, such as a lump sum of the face value of the policy plus interest, a stated monthly income for life, or a larger monthly income for a specified period (say, 10 years). Such insurance enables the insured to plan early for his retirement and have all the pre-

miums paid long before he reaches age 65. He also has life insurance protection for his family should he die before that age. The most obvious limitation of these plans are 1) the relatively small percentage of the population they reach, and 2) the relatively small amounts of insurance carried, producing a proportionately low retirement income.

The proposed Old Age Security Insurance plan suggests that life insurance companies can meet the problems of dependency and housing for the aged, within the framework of their existing practices, for a premium which will be within the reach of a large population, and yet allow profitable underwriting. This policy will literally be a security coverage; the insured will have, in effect, a usual life insurance policy, retirement benefits, and the additional security of knowing he will never have to live in uncongenial surroundings or be confined to a mental hospital or a municipal charity hospital ward. The policy could be written for the individual purchaser, but it is evident that the most productive sphere of operation, from both the social standpoint and the standpoint of the insurance company, should be group insurance.

The Old Age Security Insurance policy will incorporate the following general provisions:*

1) The insured will be entitled to the standard life insurance protection now offered under existing policies. He could, for a suitable additional premium, obtain Double Indemnity protection, waiver of premium, and the standard private aircraft and war coverages when allowable by the underwriters. He would thus have life insurance protection during the time his children are growing up, although he could not purchase as much insurance under this plan as in straight-life insurance for the premium invested. If he benefited from a group plan he could, of course, purchase more insurance for his premium since his employer also would contribute.

2) The policy would have Cash and Loan Values computed on an actuarial basis, taking into consideration the other features of the policy. However, the insurance company must be protected in the event a loan is outstanding at the time the insured becomes eligible for the security benefits outlined below.

3) Under the terms of the proposed contract, the insured could elect to receive a stated amount per thousand dollars of insurance each month for life, which amount would be larger than that granted under policies now offered the public. For reasons to be given presently, it would seem the possibility of increasing monthly payments by about 33⅓ per cent, while increasing premiums only 15 to 20 per cent, would be justified.

4) If the insured wished to receive the maximum security benefit, he is offered the option of a smaller monthly payment than in 3) above, until he is either unable or unwilling to provide his own living arrangements. At that time, he is eligible for entry into his choice of the several homes for insureds maintained by the insurance company, and his monthly income is reduced accordingly. The amount he would receive each month before entering the home could be determined upon a sound actuarial basis; however, the insurance company could in all probability prepare for his entry with a margin of around 10 per cent. This would mean, of course, the insured would receive about 10 per cent less income under this option than under option 3) above. After entry into the home, the benefits would be geared to an automatic cost-of-living or price-level formula, with appropriate deduction made for his room, board, medical expense, and so on. In cases where insurance benefits are the only income, a similarly computed minimum amount must go to the insured for small personal expenses and a modicum of pocket money. When the insured also has Social Security benefits, it would be practical for the insurance company to pay no further benefits other than home care and services, depending upon the amount of insurance carried and the current cost-of-living formula. Fluctuations in the cost of living from area to area and from time to time would make operating costs vary somewhat from home to home, but this is taken into account by the price-level formula.

5) Both an insured and his spouse could be covered under the same policy, for an appropriate premium charge, or separate policies may be written. If both are covered under one policy, they would both be entitled to entry into the home, should both survive. An option here will be that if only one so covered survives, he may elect to receive a proportional death benefit upon the demise of the spouse, or appropriate monthly payment until such time as

* It should be emphasized that the author is not an actuary; however, the plan has been discussed with insurance company officials, attorneys, and businessmen, who consider its general propositions sound.

he wishes to make use of the home benefits; his benefits would then be in accordance with 4) above. This option could be qualified either at the time the insurance is purchased or left to the surviving insured or beneficiary. In the case of dual insureds, a proportional reduction in premium will be made upon the death of one; however, the survivor must continue to pay his proportional premium until the insurance is paid up if he is to be eligible for security benefits.

6) In the event an insured wished to enter a home while an uninsured spouse still survived, if the uninsured spouse also wished to enter the home the insured would be responsible independently of the insurance company for charges for the spouse, but these charges should be made on the same basis as for the insured, outlined in 4) above. (For convenience in administration, such charges could be deducted from the insured's surplus benefit over his own living cost, if the amount of insurance he carried produced sufficient income.)

7) In the event two insureds are covered under the same policy, they must both meet the physical requirements of insurability at the time the policy is purchased. For the protection of the company, no additional insured may be added to a policy unless he or she can meet the physical requirements and a premium based upon the age at the time of addition to an existing policy is paid in advance for the period from the date of issuance of the policy to the original insured to the date the addition is made. This will prevent the company's becoming liable for payments to two insureds without having received adequate premium.

8) At the time the policy is purchased, the insured may elect that his beneficiary receive either the usual face value of the policy or the benefits outlined in either 3) or 4) above. The beneficiary will not be required to pay further premiums upon the death of the insured, if benefits 3) or 4) are chosen. However, the beneficiary must meet the same age requirements as the insured would have had to meet before being eligible for these benefits.

9) The policy must contain a provision in which the insurance company warrants that no insured or beneficiary will be committed to either a private or public mental hospital at any time after the attachment of benefit 4) above, unless qualified psychiatrists recommend this for the preservation of his life or the lives of those around him; nor will he be committed to any public or private medical hospital, other than facilities maintained by the insurance company, for any period of time longer than necessary for treatment of disease or disability which is not chronic.

10) The company will warrant that any insured may be transferred to any of the various homes maintained by the insurance company, or leave a home entirely, at his own discretion, provided a reasonable notice of his intent is given the company.

11) The insurance company will further warrant that no charges for hospital care, either mental or medical, or for medication, surgery, or other measures necessary to preserve the life of the insured, shall exceed the actual cost to the insurance company. These costs shall in no event be greater than that which would guarantee the insured his minimum pocket money, regardless of the cost to the company.

12) In the event an insured has Double Indemnity coverage, and has elected that his beneficiary receive either 3) or 4) above, such beneficiary will receive the face value of the policy at the time of the insured's death and will still be eligible for security benefits when he reaches the eligible age, without further payment of premium. When two insureds are covered under the same Double Indemnity policy, and one meets accidental death, this same provision will hold, subject to the limitations of 5) above.

It will be noted that if provision 3) is made, the insurance company has no responsibility other than money payment to the insured. At the time the insurance is written, the insured may specify the optional mode of settlement he desires. However, he would be enabled to change his option until such time as the policy is paid up, or until 5 years before he becomes eligible for security benefits, whichever occurs earlier. The contract should provide for reasonable notice to the company of the insured's intent to enter a home (for instance, 30 or 60 days), and that the insured give reasonable notice before leaving a home (see 10) above). In the case of mental patients, the request to leave the home must come through the next-of-kin or legal guardian, and is granted at the discretion of the company's psychiatrists or physicians. Section 9) above is necessary to the insurance, for commitment would destroy the security of the coverage; fear of commit-

ment, particularly to mental institutions, is hard to bear and especially important to the aged.

## HOUSING FOR AGED INSUREDS UNDER THIS PLAN

Gerontologists are familiar with the fact that, while medical advances in obstetrics and pediatrics have increased the life expectancy enormously since the turn of the century, the life span has not been significantly increased. The individual who reached age 60 in 1950 had only about 2 years greater life expectancy than his counterpart in 1900; at age 75, he had hardly a year more, and at 85 his life expectancy was no greater than a half-century ago (5, p. 57). Medical science has not yet developed highly effective preventatives or cures for the afflictions of old age. Although there has been no recent research of adequate nature, the 1935-1936 results of the National Health Survey showed that over 13 per cent of persons aged 65 and over were chronically ill at the time the survey was made (8, p. 77). Nearly all types of disability doubled for the age group 75 and over when compared with those 65-74 (5, p. 58). This fact seems singularly important; although no research of a significant nature has been conducted to obtain empirical proof, it is suggested that a much higher percentage of persons aged 65 and over who are presently in nursing homes or other institutions caring for the aged are actually 75 or over than are in the category 65-74. A disproportionate number of them are women. If the hypothesis is true, as it has every indication of being, it seems that older people maintain their own homes or otherwise manage to live in families until they reach such an advanced age that home care is inadequate or impractical. In view of the average life expectancy at advanced ages, it would seem that the actual number of insureds who would live to require care from an insurance company home might be relatively small.

One clear trend, deducible from current literature and demographic data, is that the aged prefer to remain in their own homes as long as possible and would rather live in a family situation, even with non-relatives, than be institutionalized (1, pp. 126-138). Since high rentals present difficulties to those with low incomes, it is logical to assume that provision of additional income through Old Age Security Insurance would make it possible for many insureds to continue living in their own homes until such time as they were so physically or mentally incapacitated that living alone or with a person equally aged becomes hazardous. If our hypothesis is correct, this condition would prevail for the great majority of old people *only* after they had reached an age of about 75 or over. The actual number of persons reaching this advanced age is relatively small, compared to those aged 60-74. In 1950, there were 14,415,210 people between 60 and 74, and only 3,832,395 aged 75 and over (16, table 97, p. 1-172).

Another need expressed by older people is for home services which enable them to remain in their own homes longer (17, pp. 94-100). The provision of additional income alone might not alleviate the difficulty of securing such services as part-time domestic help and shopping services; but it would at least give older people a chance to secure them. Stimulation of efforts to provide these services for stated fees might result from the ability by large numbers of older people to pay for them.

The fact that low-cost housing is particularly important to the aged is becoming recognized by architects, contractors, and private and public housing authorities (4, pp. 1-18). Low-cost housing, constructed with an eye to the special needs of the aged, by public or private authorities, may reduce the necessity of providing insurance company homes for a great many insureds.

However, the fact is that the most important security benefits under the proposed plan involve the availability of insurance company homes. Further, if such homes were available to large numbers of insureds, the present trend might be reversed, and insureds might come to prefer the relatively care-free life possible in such homes.

The insurance company could profitably invest in housing developments, which it controlled and operated, for older people. Real estate holdings, both in the form of mortgages and outright ownership, constitute an important investment income for life insurance companies. Unprofitable properties could be used to advantage in planning new developments for the use of retired insureds.

There is a wealth of literature dealing with the construction and operation of homes for the aged, and space forbids outlining details

here. However, it cannot be emphasized too much that the "brick and mortar" method is not the procedure to be used in providing the homes which will be needed. Large institution-like buildings should be avoided; when new constructions are necessary, the company should consider planning small villages or some other arrangement that could be expanded on the same piece of property, and which would be flexible enough to provide satisfactory living arrangements for insureds needing varying degrees of care and supervision (4, pp. 1-2). A structure which houses 10 to 30 persons, and not over 50, can be operated profitably; the company very possibly could use dwellings or small apartment buildings which it already owns, or which could be leased from mortagees or others, to begin the program. Such dwellings would prevent isolation of the aged insureds from community contacts, as they would be located near existing shopping centers, churches, and so on. Contrary to a fairly prevalent misconception, the aged are the least migratory segment of our population; they prefer to remain near their own communities. The insurance company should thus locate homes in strategic places, where they would be convenient to many insureds. Such areas could be determined by a survey of the policy holders. (In 1950, the areas of the United States having the greatest percentage of aged were the New England and the West North Central states; the lowest percentages were in the South and the Southwest (5, pp. 6-7, 46).)

The matter of staffing the homes will vary with the size and type of the establishment. The initial staff in small homes need not be elaborate. Such services as occupational and recreational opportunities for the retired insureds, competent medical and nursing services, psychiatric services, and so on, can be left to a competent administrator. While all insureds in a given home should be charged the same rates under the price-level index provided, there should be a scaling of homes based on luxuriousness to fit the needs and habits of various insureds.

The cost to the insurance company to operate homes will vary with location, type of home, special services available, and so on. At this writing, no cost figures were immediately available for privately operated homes for the aged outside the State of Texas. One such home, located in Fort Worth, is operated as a non-profit organization by a foundation. The home has 26 residents, in 14 rooms; none of the residents received more than the maximum $55.00 per month from Old Age Assistance, unless their relatives provided extra income. In this home, the average cost per guest per month was $51.19 in 1952. This cost included food, staff salary, utilities, laundry, and maintenance of the building and grounds. It did not include amortization of mortgage, since the grounds and building were provided by the foundation, nor did it include medical expenses. These were around $200 for the entire year for the 26 residents combined, principally for the physical examinations required of them before entry.

A privately-operated home in Austin comprised of 4 buildings, one a small hospital for chronically ill patients, which accepts a few mental patients, had a similarly low cost in 1952. The hospital, however, does not have a laboratory or surgical facilities. The entire home has room for 58 guests, and the hospital cares for 18. The approximate cost per guest per month was $45.00, which included food, laundry, utilities, staff salaries, and rent. There was a staff of 15, 9 of whom were practical nurses, in addition to the two owners. Twenty-four-hour nursing service in all buildings was given. Guests pay for their own medicine, and while this cost varies considerably, it ranged from $.50 to $10.00 per month, in addition to physician's fees.

It is quite evident that an efficiently managed privately operated home for the aged can be maintained at a comparatively more economical cost than state, municipal, or federally operated institutions.

## SOCIAL AND ECONOMIC CONSIDERATIONS

From an actuarial point of view, the increased life expectancy mentioned above has a great many implications. For example, let us consider the arbitrary definition of age 65 as that chronologic age at which people become old. Some such category was of course necessary for administrative purposes when the Social Security Act, endowment insurance, and other pensioning and retirement plans were conceived. However, it is evident that the physical and mental capacities of a significant percentage of people 65 and over are only slightly impaired. This is especially true of mental capacities, which show no particular decline until the middle seventies. Such con-

siderations have raised the interesting question of whether there should be a fixed retirement age. There are some trends toward either extending the forced retirement age beyond 65, perhaps to 70, or providing retirement and pensions on an individual basis as necessary.* The problem of providing adequate income for older people is importantly a question of preventing premature retirement, with resulting reduction of retirement costs. A raising of the age of retirement would lead to a gain in income larger than the cost of all pensions now paid to retired persons.

With such trends in mind, the actuary should carefully consider writing this insurance with several optional plans for payment of premiums and collection of benefits. Since the ability of the insurance company to underwrite the proposed insurance is based upon the availability of premiums to be invested over a long term, it is necessary that premiums be paid in a manner similar to the 20-year-paid-up policies which endow at age 65. For greater flexibility, it is suggested that policies which may be paid up in 15, 20, 25, 30, or even 35 years be offered, which will endow at ages 60, 65, 70, or 75; perhaps even wider limits could be set, with appropriate adjustments in the premium. This will make it necessary to set a maximum age beyond which the insurance could not be purchased. To enable the company to provide the extra benefits required under this insurance, it would have to be determined actuarily the number of years the company should have the use of the paid-up premiums. Then, for example, it might not be feasible to permit an insured aged 45 to purchase a 20-year-paid-up policy to endow at 65, but he might be permitted to purchase a 15-year policy at age 45 to endow at 65, or a 20-year policy to endow at age 70.

Such flexibility would be particularly important in underwriting group policies. If the employee of an insured organization could feel assured of employment to age 70, the smaller premiums possible under a 30-year-pay plan would be attractive. If such an employee, in addition, could change employers without losing his insurance coverage, the advantage to him is obvious.

A very productive application of group policies of the proposed type should be considered, keeping in mind possible funding difficulties of pension plans of employers. In 1951 about 1/6 of the 60 million people in the civilian labor force were covered by private pension plans, but few of these could look forward to receiving benefits, for only a negligible portion of the plans provided for the transfer of pension rights gained in one company's employ to another company, and nearly all of them required 10 to 25 years of service for eligibility. A serious defect in most of these private plans is that at present many are inadequately financed and might be completely liquidated by a serious business recession or the heavy burden of pensioners who shortly will be relying upon them.

The point we wish to make should be evident. If an actuarily sound group policy could be presented to a significant number of business and industrial organizations, through a large number of cooperating insurance companies, arrangement could be made for the transfer of insurance rights when an employee moved from one insured employer to another. The required number of years during which premiums would be paid could then be spent with several different employers; job opportunities would not have to be sacrificed to pension requirements. The labor force could remain as mobile as necessary to meet production and distribution needs of the economy, and still retain its retirement security. At the time an employee retired, the various insurance companies would contribute their pro rata proportion of his endowment benefits. To facilitate administration, a clearing house for this purpose could be maintained by the insurance companies on a pro rata basis proportional to their respective volumes. Reinsurance companies could also be used to advantage to give continuity of coverage to insureds.

It is almost unnecessary to point out that employers would probably find it more economical to contribute a very large share of the premiums for policies of this type, perhaps the entire sum. At the present time, many employers offer some type of group life insurance, to which they contribute at least half the premium. In addition, the employer must provide a sound method of funding if a private pension plan is offered, and this is further expense to

* The study (9, pp. 23-25) of 496 company pension plans showed that only 18.1 per cent, or 90 companies, provided for compulsory retirement at a stated age; the stated age ranged from 60 to 70 years, but age 65 was used in 79 of the plans. The other 81.9 per cent of the companies had either compulsory retirement at a later age than 65, or no compulsory retirement provisions. In the publication (1, pp. 72-80) management, unions, and farmers answered the question of fixed retirement age negatively.

him even though the employee contributes to the pension fund. Both the employee and the employer would benefit from the type of cooperation we have outlined above between employers and insurance companies. This plan could be extended to reach the smaller businesses which at the present time have a decided tendency not to provide either life insurance or pension plans (9, p. 1) An employee of a small business, which was not financially able to contribute a large portion of the premium, could begin early in his earning period to provide for his old age through large contributions to a plan of the proposed type, if he had the assurance that he would not lose his insurance coverage and endowment rights should he change employers. Such group policies would, of course, make provision for continuation of the insurance on an individual basis if the employee moved to an uninsured business. Some provisions should also be made for reinstatement of policies after periods of unemployment.

A comparison of retirement policies now being offered, with the investment of savings at an interest rate of 4½ per cent, shows certain advantages of the former. If a 20-year paid-up endowment policy in the amount of $16,000 maturing at age 65 were purchased when the insured was 25 years old, the annual premium would be $542.88; over a period of 20 years, a premium investment of $10,857.60 would be made; an annual income of $1,077.12 would be produced upon retirement.* An individual would have to invest, at 4½ per cent interest, the sum of $24,444.44 to produce an annual income of $1,100, a roughly equivalent amount. Obviously, more than twice as much capital must be invested as the sum paid in insurance premiums to produce an equivalent retirement income. It is equally obvious that the average individual aged 25 cannot carry $16,000 life insurance, for the annual premium would be out of his financial reach; however, if there were also Social Security coverage, the amount of insurance carried could safely be reduced, in view of the recently increased benefits for O. A. S. I. recipients. And of course if the insured's employer paid a substantial portion of the premium, more insurance could be carried at less cost to the insured himself.

From the insurance company's viewpoint, if the same insured in the example above lived to be 75 years of age, 10 years after the endowment policy matured, the company would pay $10,771.20 in benefits, as contrasted to the $10,857.60 in premiums received. In addition to having the investment use of the insured's premiums, accumulating annually over a period of 20 years, and which have been paid up for a second 20-year span (since the policy attached at age 25 and was thus paid up at age 45, but did not endow until age 65), the insurance company still would not pay as much in endowment benefits as it received in premiums alone, even if the insured lived to age 75, some 7 years longer than the average life expectancy in 1950.

The above figures are for one type of endowment policy which is at present offered the public. Since the premiums for the proposed Old Age Security Insurance would be slightly higher to begin with, it is apparent that the insurance company could provide the benefits necessary under this proposed coverage in accordance with sound underwriting practices. This would be particularly true if the company considered carefully the possibility of a smaller profit in order to reach a much larger market. The insurance should be made practical for families in the $2,000 to $5,000 annual income categories. In 1955 there were over 20 million of these families, comprising nearly half of the nation's 41½ million families (14, p. 15). There were also 3 million unrelated individuals in this income bracket. Since the majority of these people live in urban areas, it is safe to assume that a predominant proportion of them are employees of business and industrial organizations which might find group policies advantageous. If this plan were made attractive to those with lower incomes, it should certainly reach also the people in the higher income brackets, for these are already most fully aware of endowment insurance.

It is the people of the American middle-class, those whose peak earnings seldom exceed $3,500, those who spend their productive years as wage earners or low-salaried personnel in business or industry, who find it so difficult to meet their current obligations and still provide for their own old age. It follows that these are the people who will fall into the excessively low income groups when their productive years are over and who constitute the

* This premium includes waiver of premium provisions, but does not provide double indemnity. The name of the company underwriting this policy will be provided upon request. The endowment benefit pays $61.32 annually per thousand dollars insurance for life, after age 65; slightly more for ten years certain.

problem of dependency. If extensive cooperation among employers and insurance companies could provide Old Age Security Insurance as herein outlined for a significant number of these people, at a cost which could be contributed from their earnings without depriving their growing families, a considerable part of the dependency problem could be solved. The benefits from Old Age Security Insurance, combined with Old Age and Survivors Insurance, would provide them a truly secure old age without endangering the national economy or requiring a disproportionate share of total industrial production to maintain pensions.

Moreover, extensive utilization of such a plan would tend to eliminate at least part of the problem presented by the rapidly increasing rate of admission of the dependent aged into state mental hospitals. Overcrowding of mental hospitals with aged persons who are sometimes not mentally ill, or, if they are, seem to be suffering from degenerative afflictions for which hospital confinement or treatment hold little hope of cure, not only prevents application of the hospital's limited treatment facilities to younger patients who might be helped but at the same time often condemns the aged persons to lives of neglect and personal unhappiness. Such misuse of mental hospital facilities is an expensive waste of state and federal funds and of professional and service personnel. Indeed one student of mental hospital organization (3, pp. 204-212) suggests decentralized small homes caring for a limited number of persons, homes placed in or near the community where relatives and friends still reside, would make it possible for the aged individual to have the care his age or infirmities require without losing contact with his local community and previous social relationships.

In modern urban families, it is sometimes financially, physically, as well as emotionally, impossible for an aged member to be cared for in the home. Enabling the aged person to be financially independent and assuring him of the opportunity to remain near his family and friends even after he can no longer live alone, would frequently enrich the lives of both the aged person and his family.

## SUMMARY

Two of the problems most urgently requiring solution for the increasing population of persons aged 65 and over in the U. S. are dependency and housing. The proposed Old Age Security Insurance offers a plan whereby insurance companies can partially solve these problems, within the framework of established patterns of insurance underwriting and of business and industrial pension plans.

The maximum benefits under this proposed plan would include life-long care in homes for the aged, owned and operated by the insurance company. The plan is flexible, with a variety of retirement ages. It is modeled along the lines of existing 20-year paid-up, endowment at age 65 life insurance policies. There are, however, important modifications. Chief among these is its adaptability to group insurance programs, thus eliminating the necessity for pensions or retirement plans financed by business and industrial firms. An important feature is a reinsurance plan which would enable an employee in insured organizations to continue his coverage even when he changed employers. This proposed insurance would supplement, rather than replace, Old Age and Survivors Insurance. The construction and maintenance of homes for the aged insureds in strategic locations will avoid overcrowding of state mental hospitals with indigent, but sane, aged persons. The plan is outlined in detail, but no actuarial tables have been computed. Very careful actuarial work, as well as research concerning the potential market, will be required to develop the plan fully.

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# BOOK REVIEWS

HORIZONS FOR OLDER PEOPLE, by George Gleason. The Macmillan Co., New York, 1956, 137 pages, $2.95.

"How can my church meet its full responsibility for the joyful living and usefulness of the 14,000,000 older people of this country?" This is the question Dr. George Gleason poses to the reader of *Horizons for Older People*. Dr. Gleason writes with the authority of a person who through eighty-one years of living knows his subject.

The main focus of this book is the church and the older person. What should the church be doing for its older members and what should be the role of the older person in the church? Through the use of examples drawn from church activities throughout the United States and Canada, Dr. Gleason illustrates how some church organizations are attempting to answer these questions. He presents in a very practical manner some of the many areas in which the life of the older person may be related to the life of the church and the wider community.

After a brief overview of aging in general and its relationship to the church in particular, Dr. Gleason presents possibilities for group activities for older people which can be developed within the church setting. This is followed by a discussion of the personal needs of those in their later years. In many ways this is the most insightful section of this publication. Here we find raised the kinds of situations which must be realistically understood, if we are going to provide adequate leadership and programs for our aging citizens. In this section ideas and suggestions are made concerning retirement, financial security, health, housing, and recreation and hobbies. This is followed by a discussion as to the ways in which the older person can serve both his church and his community.

For the reader who is looking for specific information relating to ways of meeting the needs of older persons, the appendices of this publication are notable. Dr. Gleason, through extensive correspondence and investigation has compiled much material relating to such topics as: Selecting Resources for Group Leaders, Names Used by Older Adult Groups, Volunteer Services to the Church, Volunteer Services to the Community, Suggestions for a Personal-Interests Questionnaire, Homes for the Aging (with a helpful warning on important points for a group to consider before embarking on a housing venture), and a Bibliography, annotated by topics. These appendices contain names and addresses as to where to write for specific information.

Dr. Gleason's publication draws together much practical information as to what many churches and other organizations are doing in meeting the challenge of an aging population. It should serve as a helpful aid to many groups who are just beginning to become aware of their responsibilities in this area.

WALTER M. BEATTIE, JR.
Lindenwood College
St. Charles, Missouri

THE ECONOMIC STATUS OF THE AGED, by Peter O. Steiner and Robert Dorfman. University of California Press, Berkeley, 1957. 293 pages, $5.00.

This monograph is a survey of the economic condition of the aged, the purpose of which is to determine factually the interrelationship of variables bearing on this status. The study is based primarily upon data collected by the Bureau of the Census in 1952 from a nationwide sample which included 3,000 households containing persons 65 and over.

It presents in a clear and concise manner a large number of excellent tables, both in the text and an appendix, cross-classifying sociologic and economic variables, which tables will doubtless be of great use as source material for gerontologists. The authors are precise in their definitions and usage of terms. Some of the important variables considered are three types of "economic units" (couples, unrelated males, and unrelated females), the normal occupation, i.e., the "longest occupation" followed, labor force status, income and receipts, which are defined differently to permit detailed analyses, and living arrangements.

One interesting finding is that aged men and women who are not in the labor force apparently have little interest in obtaining employment (only 6 per cent of such men over 65 were interested in full- or part-time work). After a careful analysis of both monetary and non-monetary receipts, the authors show that despite public assistance programs, roughly 10 to 20 per cent of the aged are existing with receipts below subsistence budget levels and yet receive no assistance. Both dependency and use of savings and assets for current expenses were higher for unrelated females than for unrelated males, and lowest of all for couples. On the other hand, insurance holdings and liquid assets were higher for couples than for the other two types of economic units. However, the authors point out that the economic advantages enjoyed by aged couples are not usually transferable to the widow if the husband dies.

The authors show throughout the monograph that the aged population is not a homogeneous one; that more attention should be given to the economic problems of aged women, and that prevention of the obsolescence of skills would alleviate many of the economic problems of aged men. This book should clarify many questions and misconceptions concerning the economic condition of the aged and prove of interest and value to all persons dealing with such problems.

FRANCIS GILLESPIE SCOTT
University of California
Los Angeles

A POSITIVE POLICY TOWARD AGING, Report of New Jersey Old Age Study Commission. Trenton, February 1956, x + 217 pp., paperbound.

This excellent volume might well serve as a model for reports of its kind. It grew out of a two-year study by a seven-member commission created by the New

Jersey State Legislature and headed by Senator Walter H. Jones. Information obtained in public hearings and from the literature, together with recommendations, is presented in an admirably integrated fashion.

The major divisions deal with the arithmetic of aging in New Jersey, economics, health, education, recreation, religion, and housing and living arrangements. Care is taken, through emphasis on interrelationships, to avoid creating excessive compartmentalization. Moreover, the report is not marred by extreme localism.

Two basic conclusions emerged: (1) study and observation of the aging process should be made a continuous function and (2) co-ordination of all resources must be achieved to develop an optimum program. Accordingly the Study Commission recommends establishment of (1) a professionally staffed, permanent Commission on Aging as a division of the Department of State; (2) a Citizens Council on Aging to channel information and serve as liaison between and among the state's private resources; and (3) a pattern for Community Councils on Aging throughout the state. Enabling legislation for the Commission on Aging and the Citizens Council is provided in the concluding section.

IRVING L. WEBBER
Institute of Gerontology
University of Florida
Gainesville

TOWARD GOOD HOUSING FOR THE AGING, Selected Articles from the *Journal of Housing*. Publication N 394, National Association of Housing and Redevelopment Officials, 1313 E. 60th Street, Chicago 37, December, 1956, 40 pages, paperbound, $1.00.

The reprints from the *Journal of Housing* brought together in this booklet appeared from 1946 through 1956. They are grouped under 6 headings: early thinking, federal legislation, state and local efforts, experience, design, and community services. A short annotated reference list of books and articles on housing for the aging is appended. Publication of this material is intended to point up earlier theoretic analyses and significant developments during the decade.

Although a good deal of useful information is offered, the presentation is generally unsystematic and chronologically unsequential even in some instances where more than one report of a project is included. The discussions by John P. Dean and Hertha Kraus, originally published in 1946 and 1950, have considerable historical interest. Despite its shortcomings, the publication does demonstrate well the mushrooming of interest and action during the ten-year period.

IRVING L. WEBBER
Institute of Gerontology
University of Florida
Gainesville

STUDIES OF THE AGED AND AGING, compiled by the staff of the Committee on Labor and Public Welfare, U. S. Senate. U. S. Government Printing Office, Washington, D. C., 1956-1957.

The Committee studies, in 11 volumes, only the first 9 of which were available at the time of this review, provide an excellent coverage of the problems of aging. The scope of these studies is indicated by the titles to the separate volumes listed below. There is, in addition to those volumes, a summary of Federal Statutory Provisions Affecting Older Persons, issued earlier as a separate pamphlet. The series, running over 1800 pages, was prepared for the use of the Committee on Labor and Public Welfare.

This will become a very valuable library for workers in the field, for it brings together most of the important information scattered elsewhere in many volumes. One illustration of this is Volume VII, *Guide to Significant Publications*, which, under significant headings, presents abstracts of books and articles, both national and international of fairly recent date, many of which, especially the articles, would be difficult to obtain.

The titles of the volumes show the extent of coverage:

1. Federal and State Activities
2. Health and Health Services
3. Income and Income Maintenance
4. Employment
5. Public and Private Services for Older People, including rehabilitation, housing and living arrangements, education, and community services
6. Care of the Aging by the Veterans' Administration
7. Guide to Significant Publications (an extensive Bibliography covering not only important books and pamphlets but articles in professional and other journals.)
8. Population: Current Data and Trends
9. Research, Demonstration, and Training
10. Surveys of State and Local Projects
11. Fact Book on Aging

The monthly magazine, *Aging*, announced earlier that individual volumes might be had free by writing the Committee on Labor and Public Welfare, U. S. Senate, Washington 25, D. C.

WILLIS H. REALS
Washington University
St. Louis

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*Hospital Patient Survey*, The New York Foundation, New York, 1956, 146 pages, multilithed, spiral bound.

*Mobilizing Resources for Older People*, Proceedings of the Federal-State Conference on Aging, June 5, 6, 7, 1956, Washington, D. C., sponsored by Council of State Governments—Federal Council on Aging, 1957, 120 pages, paper bound.

*Pastoral Ministry to Families*, by John Charles Wynn, The Westminster Press, Philadelphia, 1957, 214 pages, $3.75. Chapter 7, Three Special Problems in Pastoral Care: part I: Families and Their Aged Persons, pp. 153-165.

*Psychological Development Through the Life Span*, by Sidney L. Pressey and Raymond G. Kuhlen, Harper & Brothers, New York, 1957, 654 pages, $6.00.

*Retirement Policies Under Social Security*, by Wilbur J. Cohen, University of California Press, Berkeley, 1957, 105 pages, $3.00.

*Union Policy and the Older Worker*, by Melvin K. Bers, University of California Press, Berkeley, 1957, 87 pages, $1.00.

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# JOURNAL OF GERONTOLOGY

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## Section C

## Index to Current Periodical Literature

VOLUME 12, SECTION C JULY, 1957 NUMBER 3

# INDEX TO CURRENT PERIODICAL LITERATURE

NATHAN W. SHOCK

*Gerontology Branch*
*National Heart Institute*
*National Institutes of Health*

THE SUBJECT categories are those in *A Classified Bibliography of Gerontology and Geriatrics* by Nathan W. Shock published by Stanford University Press, Stanford, California (1951). Only major headings are used and the Roman numerals correspond to those given in the bibliography. In so far as possible, references are classified according to organ systems. Thus, most of the material on Geriatrics will be found under the organ system involved in the disease. Cross references are indicated by number at the end of each section. When available, abstract references are given *(B.A.—Biological Abstracts: P.A.—Psychological Abstracts,* and *P.I.—Population Index).* Abbreviations for journals are those used in *A World List of Scientific Periodicals Published* in the years 1900-1933, 2nd Edition. For journals not listed, abbreviations were devised according to the general rules used in the above source. It is impossible to cover all journals and list all papers concerned with aging and the aged. Authors and publishers are requested to call attention to publications or to send reprints to the Gerontology Branch, Baltimore City Hospitals, Baltimore 24, Maryland. The assistance of the Forest Park Foundation, Peoria, Illinois, in the preparation of these materials is gratefully acknowledged.

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